Supporting Information

Total Synthesis of (+)-SCH 351448: Efficiency *via* Chemoselectivity and Redox-Economy Powered by Metal Catalysis

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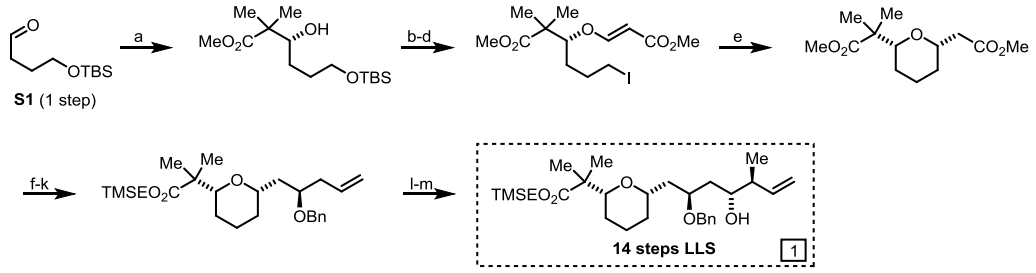
Contents:

Summaries of Previous Syntheses:

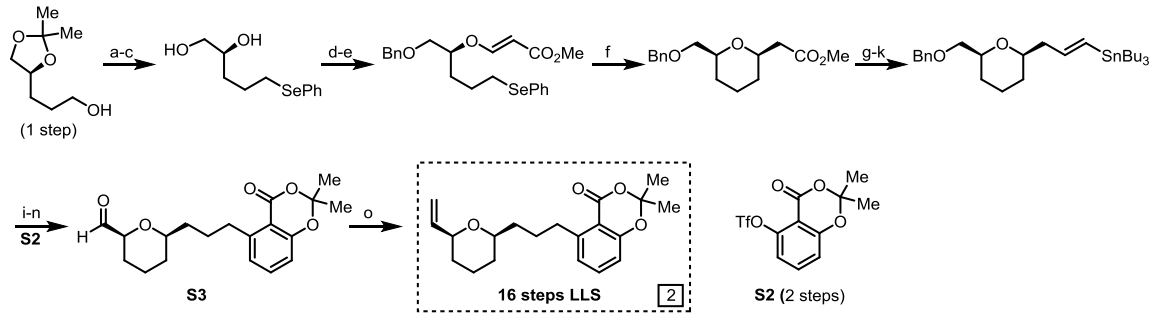
A. Lee *et al. J. Am. Chem. Soc.* **2004**, *126*, 2680.; *J. Org. Chem.* **2005**, *70*, 6321.

Fragment 1



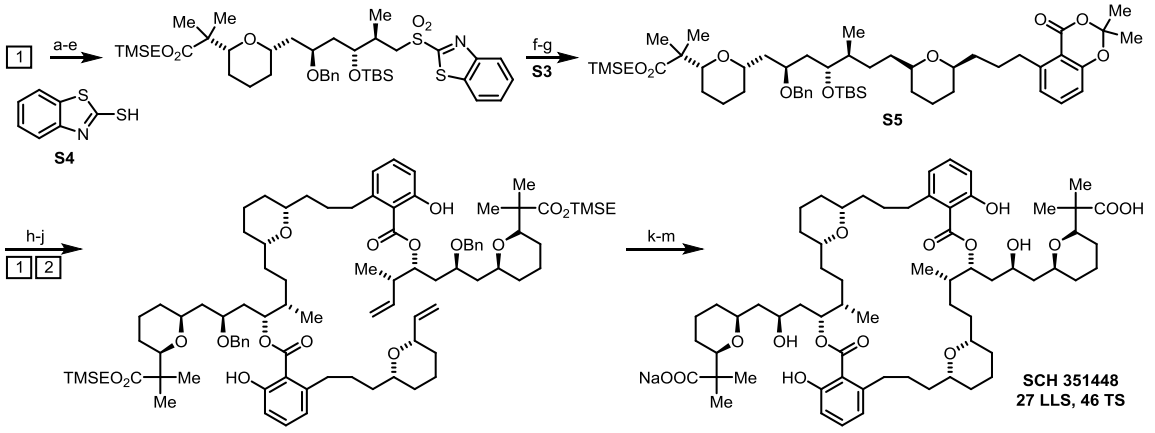
Key: (a) *N*-tosyl-(*S*)-valine, BH_3-THF, DCM; **S1**, $Me_2CC(OMe)(OTMS)$, -78°C; (b) $CHCCO_2Me$, NMM, MeCN; (c) concentrated HCl, MeOH; (d) I_2, Ph_3P, imidazole, THF, 0 °C; (e) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH; (f) KOH, THF-H_2O-MeOH (3:1:1); (g) BH_3-DMS, $B(OMe)_3$, THF, 0 °C; (h) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (i) $CH_2CHCH_2B(^{l}Ipc)_2$, ether, -78 °C; NaOH, H_2O_2, reflux; (j) NaHMDS, BnBr, THF-DMF (4:1), 0 °C to room temperature; (k) $Ti(O\textit{i}\text{-}Pr)_4$, $TMSCH_2CH_2OH$, DME, 120 °C; (l) OsO_4, NMO, acetone-H_2O (3:1); $NaIO_4$; (m) (*E*)-$CH_3CHCHCH_2B(^{d}Ipc)_2$,THF, -78 °C; NaOH, H_2O_2, -78 °C to room temperature.

Fragment 2



Key: (a) TsCl, TEA, DCM, 0 °C; (b) PhSeSePh, $NaBH_4$, EtOH; (c) concentrated HCl, MeOH; (d) Bu_2SnO, benzene, reflux (-H_2O); BnBr, TBAI, benzene, reflux; (e) $CHCCO_2Me$, NMM, MeCN; (f) *n*-Bu_3SnH, AIBN, benzene (0.01 M), reflux; (g) LAH, THF, 0 °C; (h) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (i) CBr_4, HMPT, THF, -30 °C; (j) *n*-BuLi, THF, -78 °C; (k) *n*-Bu_3SnH, AIBN, benzene (0.02 M), reflux; (l) $PdCl_2(PPh_3)_2$, **S2**, LiCl, Ph_3P, DMF (0.1 M), 120 °C; (m) H_2, Pd/C, MeOH; (n) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (o) Ph_3PCH_3+Br-, *n*-BuLi, THF, 0 °C; **S3**, -78 °C to room temperature.

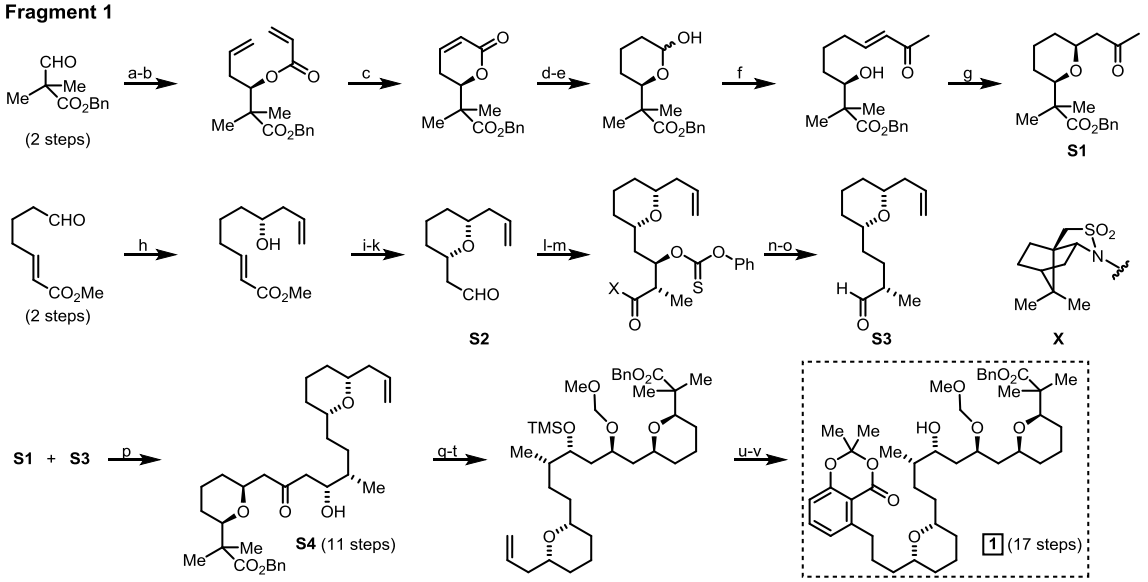
Fragment Union and End Game



Key: (a) TBSOTf, 2,6-lutidine, DCM, 0 °C; (b) OsO_4, NMO, acetone-H_2O(3:1); $NaIO_4$; (c) $NaBH_4$, EtOH; (d) **S4**, DIAD, Ph_3P, THF, 0 °C; (e) $(NH_4)_6Mo_7O_{24}$-$4H_2O$, H_2O_2, EtOH, 0 °C to room temperature; (f) NaHMDS, ether, -78 °C; **S3** (syringe pump, 30 min), -78 °C to room temperature; (g) $TsNHNH_2$, NaOAc, DME-H_2O (1:1), reflux; (h) NaHMDS, THF, 0 °C; **1**; (i) concentrated HCl, MeOH; (j) NaHMDS, THF, 0 °C; **2**, 0 °C; (k) 10 mol % Grubbs' catalyst (2nd generation), DCM (3 mM), 80 °C; (l) H_2, Pd/C, MeOH-EtOAc (3:1); (m) TBAF, THF; 4 N HCl (saturated with NaCl).

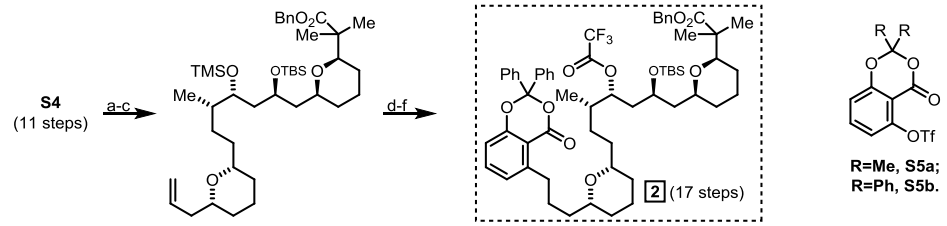
B. De Brabander *et al. Org. Lett.* **2002**, *4*, 481.; *Org. Lett.* **2005**, *7*, 2791.

Fragment 1



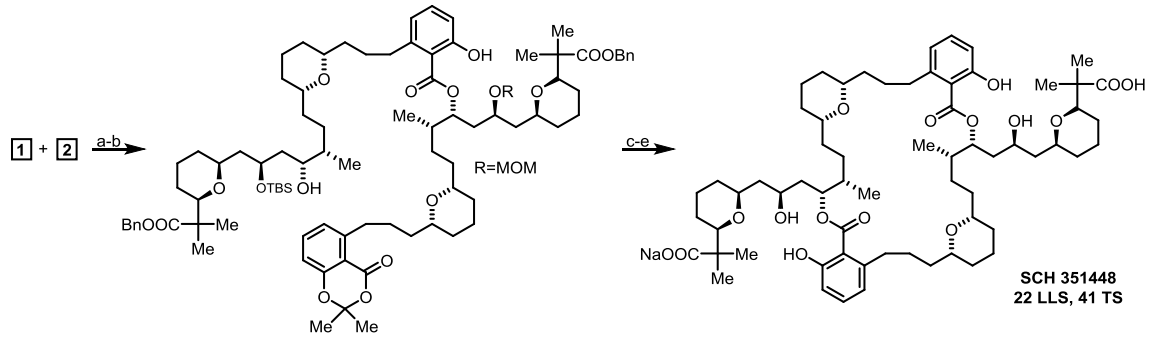
Key: (a) (+)-Ipc$_2$BOMe, allylMgBr, -78 °C, Et$_2$O; (b) CH$_2$=CHCOCl, *i*-Pr$_2$NEt, DMAP,CH$_2$Cl$_2$; (c) 5 mol % Grubbs' 2nd generation catalyst, CH$_2$Cl$_2$, 4 h, rt; (d) NiCl$_2$-6H$_2$O, NaBH$_4$, THF, 0 °C, 2 h; (e) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 1 h; (f) 1-triphenylphosphoranylidene-2-propanone, MeCN, 90 °C, 24 h; (g) *t*-BuOK, THF, 0 °C, 5-10 min; (h) *B*-allyl bis(4-isocaranyl)borane, Et$_2$O, -78 °C; (i) *t*-BuOK, THF, -35 °C; (j) LiAlH$_4$, Et$_2$O, 0 °C; (k) PCC, CH$_2$Cl$_2$, 3 h, RT; (l) (2*S*)-*N*-propionyl bornanesultam, TiCl$_4$, *i*-Pr$_2$NEt, -78 °C; then add **S2**, -78 °C; (m) PhOC(S)Cl, py, CH$_2$Cl$_2$, 14 h, RT; (n) Bu$_3$SnH, 10% AIBN, PhH, 7 h, reflux; (o) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 1 h; then MeOH, -78 °C, 10 min; or LiAlH$_4$, Et$_2$O; then Dess-Martin periodinane, CH$_2$Cl$_2$; (p) Et$_2$BOTf, Et$_2$O, -78 °C; then **S3** -78 °C; (q) MeCHO, SmI$_2$, THF, -10 °C; (r) MOMCl, ^{i}Pr$_2$NEt, DCM; (s) K$_2$CO$_3$, MeOH; (t) TMSCl, NEt$_3$, DCM; (u) 9-BBN, THF; **S5a**, PdCl$_2$dppf, aq. K$_3$PO$_4$, DMF/THF; (v) HF-py, THF.

Fragment 2



Key: (a) Me$_4$N(AcO)$_3$BH, HOAc, MeCN, -10 °C; (b) TBSCl, imid., DMF; (c) TMSCl, NEt$_3$, DCM; (d) 9-BBN, THF; **S5b**, PdCl$_2$dppf, aq. K$_3$PO$_4$, DMF/THF; (e) HF-py, THF; (f) TFAA, py, DCM.

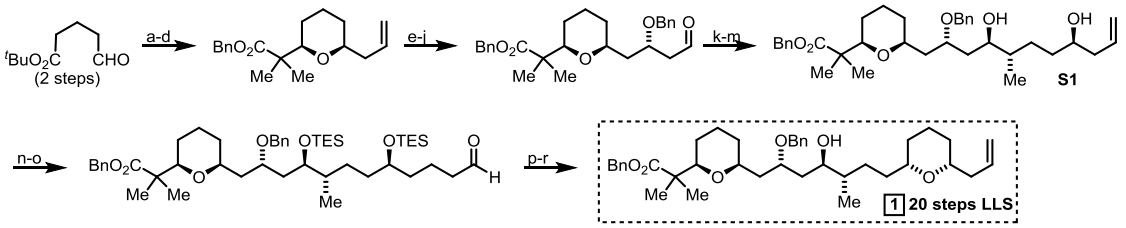
Fragment Union and End Game



Key: (a) h*v* (300 nm), DCM, 0.1 M, 1 h, rt; (b) NH$_3$, MeOH; (c) NaHMDS, THF, -78 °C; (d) 10% Pd/C, H$_2$, MeOH; (e) 48% aq. HF, MeCN, rt, 48 h; hexane extraction from aq. HCl (4 N, sat. with NaCl).

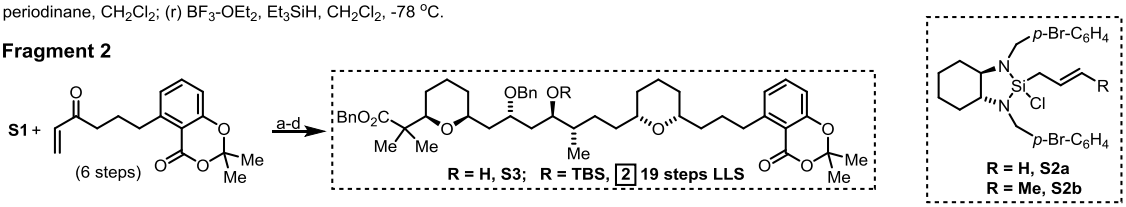
C. Leighton *et al. Org. Lett.* **2005**, *7*, 3809.

Fragment 1



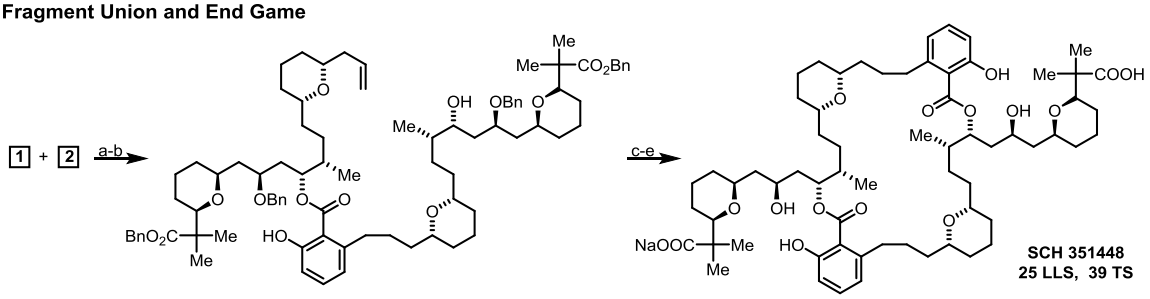
Key: (a) *ent*-**S2a**, -10 °C, CH_2Cl_2; (b) *p*-TsOH, PhH, reflux; (c) $BnO_2CCH(CH_3)_2$, LDA, THF, 0 °C; (d) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C; (e) OsO_4, NMO, Acetone, H_2O; (f) $NaIO_4$, THF, H_2O; (g) (+)-*B*-methoxyldiisopinocamphenylborane, AllylMgBr, Et_2O, -100 °C; (h) NaH, BnBr, DMF, 0 °C; (i) OsO_4, NMO, Acetone, H_2O; (j) $NaIO_4$, THF, H_2O; (k) **S2b**, CH_2Cl_2, 0 °C; (l) $(Allyl)_2Si(NEt_2)H$, CH_2Cl_2; (m) $Rh(acac)(CO)_2$, 900 psi CO, PhH, 65 °C, *n*-Bu_4NF, THF, reflux; (n) TESCl, Et_3N, CH_2Cl_2, -78 °C; (o) $Rh(acac)(CO)_2$, NIXANTPHOS, 600 psi H_2/CO, THF, 60 °C; (p) AllylBr, Zn, aq. NH_4Cl, THF; (q) Dess-Martin periodinane, CH_2Cl_2; (r) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C.

Fragment 2



Key: (a) Grubbs' II Cat., CH_2Cl_2, reflux; (b) Lindlar Cat., H_2, MeOH; (c) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C; (d) TBSOTf, Et_3N, CH_2Cl_2.

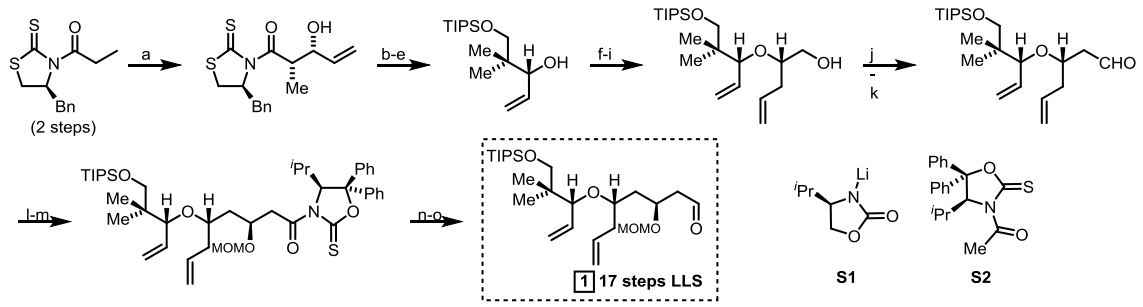
Fragment Union and End Game



Key: (a) **2**, NaHMDS, THF, 0 °C; then **3**; (b) HCl, Et_2O, MeOH; (c) **S3**, NaHMDS, THF, 0 °C; (d) Grubbs' II Cat., CH_2Cl_2, reflux; (e) Pd/C, H_2, MeOH, EtOAc.

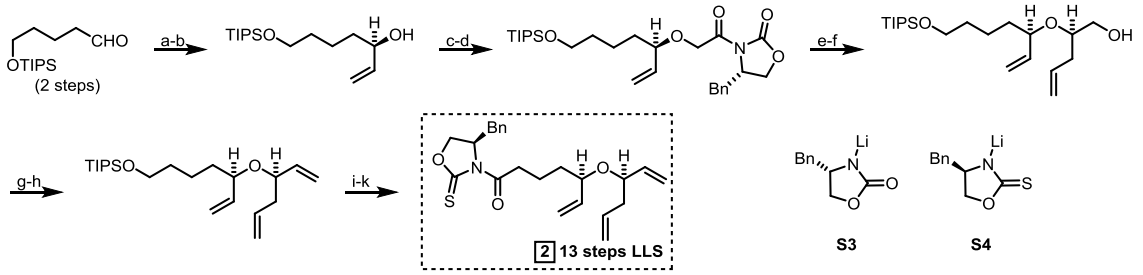
D. Crimmins *et al. Org. Lett.* **2006**, *8*, 2887.

Fragment 1



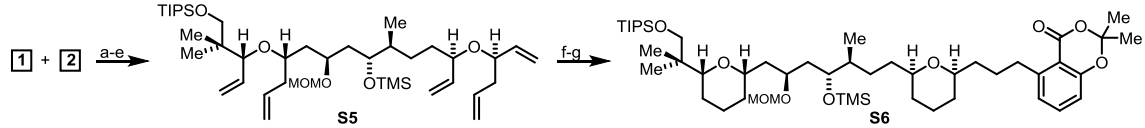
Key: (a) $TiCl_4$, (-)sparteine, NMP, acrolein, CH_2Cl_2, -78 °C; (b) ^{t}BuOH, imidazole; (c) LDA, MeI, THF, -30 °C; (d) $LiAlH_4$, Et_2O, (e) TIPSCl, imidazole; (f) $BrCH_2Co_2H$, NaH; (g) **S1**, PivCl, THF; (h) $NaN(SiMe_3)_2$, THF, allyl iodide, -40 °C; (i) $LiBH_4$, MeOH, Et_2O; (j) $Me_2CCN(OH)$, DEAD, Ph_3P, THF; (k) ^{i}Bu_2AlH, CH_2Cl_2; (l) **S2**, $TiCl_4$, (-)-sparteine, NMP, CH_2Cl_2, -78 °C; (m) MOMCl, CH_2Cl_2, ^{i}Pr_2NEt, 0 °C; (n) $LiBH_4$, MeOH, Et_2O; (o) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.

Fragment 2

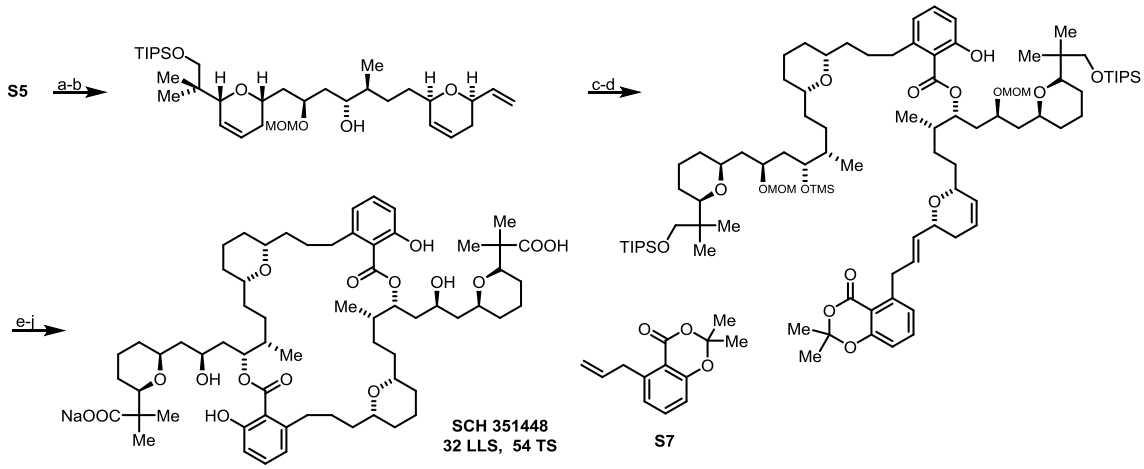


Key: (a) CH_2=CHMgBr, THF; (b) $Ti(O^iPr)_4$, (+)-DCHT, ^{t}BuOOH, CH_2Cl_2; (c) $BrCH_2CO_2H$, NaH, THF; (d) **S3**, PivCl, THF; (e) $NaN(SiMe_3)_2$, THF, allyl iodide, -40 °C; (f) $LiBH_4$, MeOH, Et_2O; (g) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (h) Ph_3PCH_3Br, ^{t}BuOK, $PhCH_3$; (i) ^{n}Bu_4NF, THF, (j) H_2CrO_4, acetone; (k) **S4**, $(COCl)_2$, DMF, CH_2Cl_2.

Fragment Union and End Game



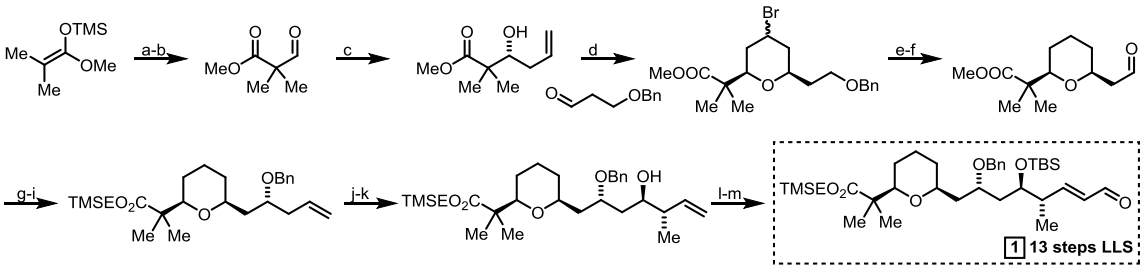
Key: (a) **1**, $TiCl_4$, (-)-sparteine, NMP, CH_2Cl_2, -78 °C; (b) TMSCl, Et_3N, DMAP, CH_2Cl_2; (c) $NaBH_4$, THF, H_2O; (d) MsCl, Et_3N, CH_2Cl_2; (e) $LiEt_3BH$, THF; (f) **S7**, $Cl_2(PCy_3)(IMes)Ru$=CHPh, CH_2Cl_2, 40 °C; (g) Rh/Al_2O_3, H_2.



Key: (a) PPTS, MeOH, 0 °C; (b) $Cl_2(PCy_3)(IMes)Ru$=CHPh, CH_2Cl_2, 40 °C; (c) **S6**, $NaN(SiMe_3)_2$, THF; (d) **S7**, $Cl_2(PCy_3)(IMes)Ru$=CHPh, CH_2Cl_2, 40 °C; (e) Rh/Al_2O_3, H_2; (f) PPTS, MeOH; (g) NaHMDS; (h) ^{n}Bu_4NF, THF; (i) TPAP, NMO; $NaClO_2$; (j) HF, CH_3CN, 4N HCl, NaCl.

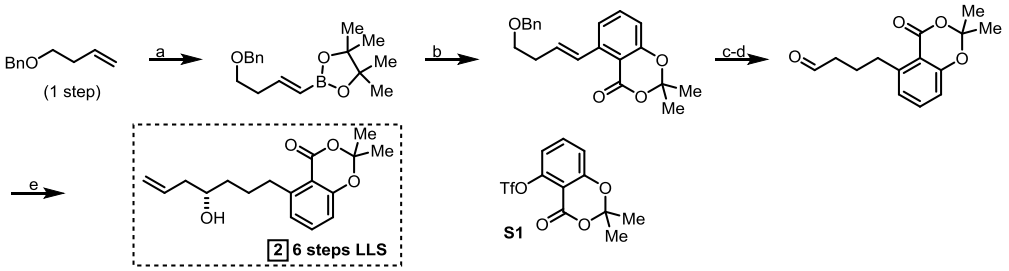
E. Loh *et al. Chem. Commun.* **2007**, 939.

Fragment 1



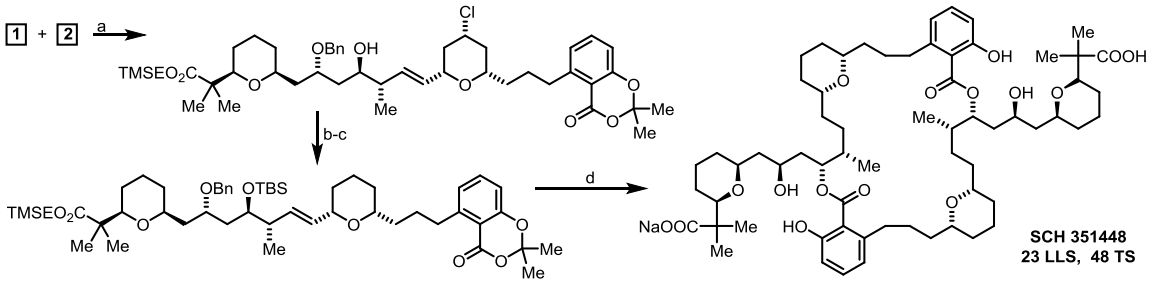
Key: (a) HCOH, $InCl_3$, 24 h; (b) PCC, CH_2Cl_2, 0 °C, 12 h; (c) (+)-DIPBr, AllylMgBr, -78 °C; (d) $InBr_3$, TMSBr, -78 °C; (e) Pd/C, $NaHCO_3$, H_2, 24 h; (f) DMP, CH_2Cl_2, 0 °C, 0.5 h; (g) (+)-DIPBr, AllylMgBr, THF, -78 °C; (h) BnBr, NaH, DMF, 0 °C, 0.5 h; (i) $Ti(O^iPr)_4$, TMSEOH, reflux, 48 h; (j) OsO_4, NMO, 12 h, then $NaIO_4$, 0.5 h; (k) ^{n}BuLi, (*E*)-But-2-ene, KO^tBu, $B(^dIpc)_2OMe$, BF_3-OEt_2, -78 °C; (l) Acrolein, Hoveyda-Grubbs' II Cat., CH_2Cl_2, reflux, 12 h; (m) TBSOTf, 2,6-Lutidine, Et_3N, 0 °C, 0.5 h.

Fragment 2



Key: (a) Grubbs' II Cat., CH_2Cl_2, reflux, 8 h; (b) **S1**, $Pd(dppf)Cl_2$, K_3PO_4, THF, reflux, 12 h; (c) Pd/C, H_2, 4 h; (d) DMP, 0 °C, 0.5 h; (e) (+)-DIPBr, AllylMgBr, -78 °C.

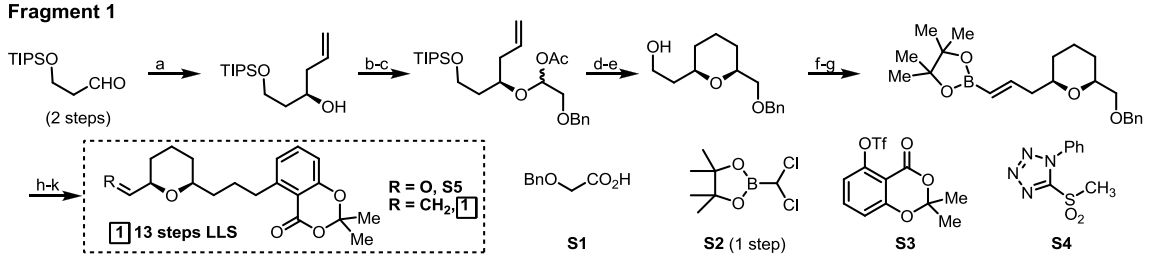
Fragment Union and End Game



Key: (a) $In(OTf)_3$, TMSCl, CH_2Cl_2, -78 °C to -40 °C, 4 h; (b) ACCN, Bu_3SnH, PhMe, reflux, 12 h; (c) TBSOTf, 2,6-Lutidine, Et_3N, 0 °C, 0.5 h; (d) Lee *et al. J. Am. Chem. Soc.* **2004**, *126*, 2680.; *J. Org. Chem.* **2005**, *70*, 6321.

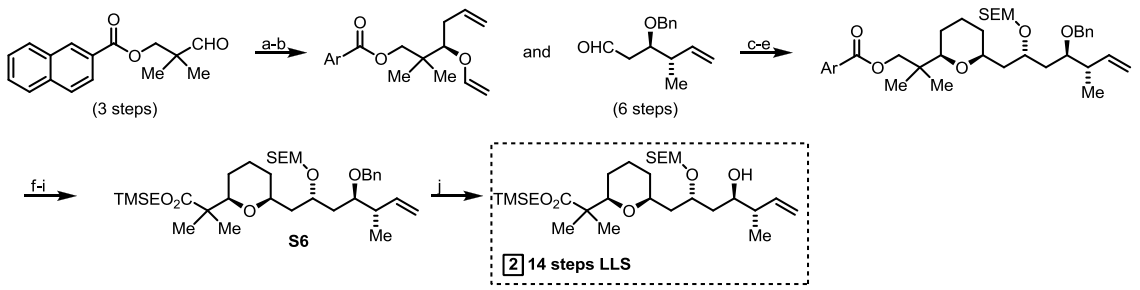
F. Rychnovsky *et al*. *Org. Lett*. **2008**, *10*, 3101.

Fragment 1



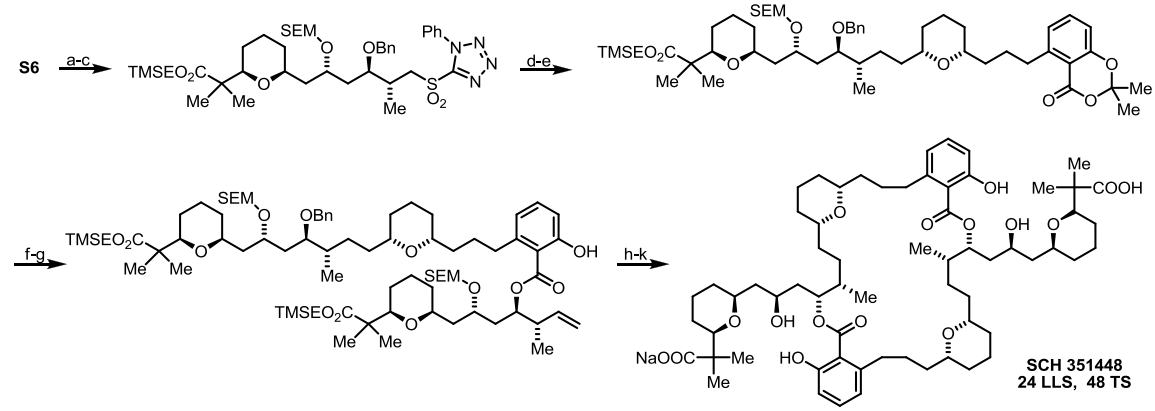
Key: (a) AllylSnBu$_3$, Ti(O^{i}Pr)$_4$, (*R*)-BINOL; (b) **S1**,DCC, DMAP; (c) DIBAL-H; Ac$_2$O, DMAP; (d) SnBr$_4$, -78 ^{o}C; (e) Bu$_3$SnH, NaBH$_4$, EtOH; then 3 N HCl; (f) DMP, CH$_2$Cl$_2$; (g) CrCl$_2$, LiI, **S2**, THF; (h) **S3**, PdCl$_2$(dppf), K$_3$PO$_4$, THF; (i) Pd/C, H$_2$, MeOH; (j) DMP, CH$_2$Cl$_2$; (k) **S4**, NaHMDS.

Fragment 2



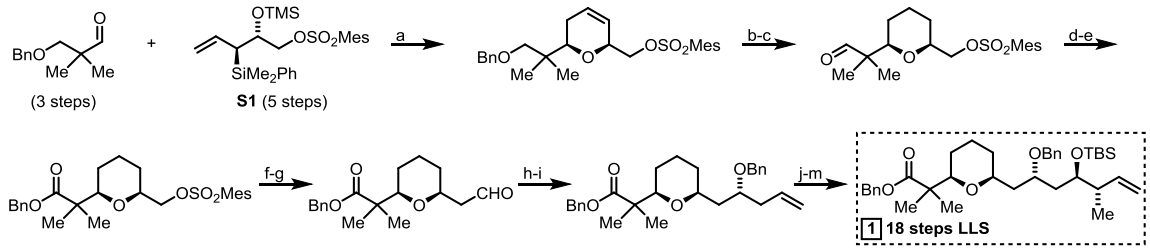
Key: (a) AllylTMS, TiF$_4$, (*R*)-BINOL; (b) Ethyl vinyl ether, Hg(TFA)$_2$; (c) TiBr$_4$, 2,6-DTBMP, CH$_2$Cl$_2$, -78 ^{o}C; (d) Bu$_3$SnH, AIBN; (e) SEMCl, DIPEA; (f) NaOH, MeOH; (g) TPAP, NMO; (h) NaClO$_2$, NaH$_2$PO$_4$, 2-methyl-2-butene; (i) TMSCH$_2$CH$_2$OH, DIAD, PPh$_3$; (j) DDQ, pH 7 buffer, CH$_2$Cl$_2$.

Fragment Union and End Game



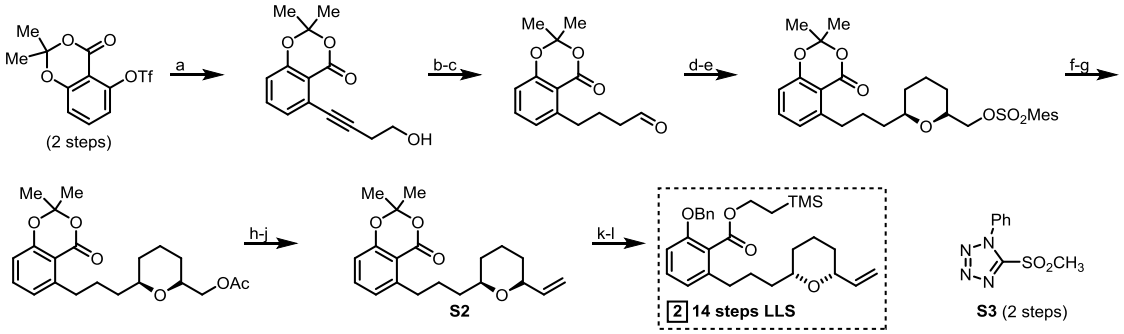
Key: (a) O$_3$, CH$_2$Cl$_2$, -78 ^{o}C; PPh$_3$; NaBH$_4$; (b) PPh$_3$, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol; (c) 30% H$_2$O$_2$, EtOH, (NH$_4$)$_6$Mo$_7$O$_{24}$-4H$_2$O; (d) **S5**, NaHMDS, THF; (e) *p*-TsNHNH$_2$, NaOAc, 100 ^{o}C; (f) **2**, NaHMDS; (g) DDQ, pH 7 buffer; (h) **1**, NaHMDS, THF; (i) Grubbs-Hoveyda Cat., CH$_2$Cl$_2$, reflux; (j) *p*-TsNHNH$_2$, NaOAc, 100 ^{o}C; (k) TFA, CH$_2$Cl$_2$; 4 N HCl, NaCl, hexanes.

Fragment 1



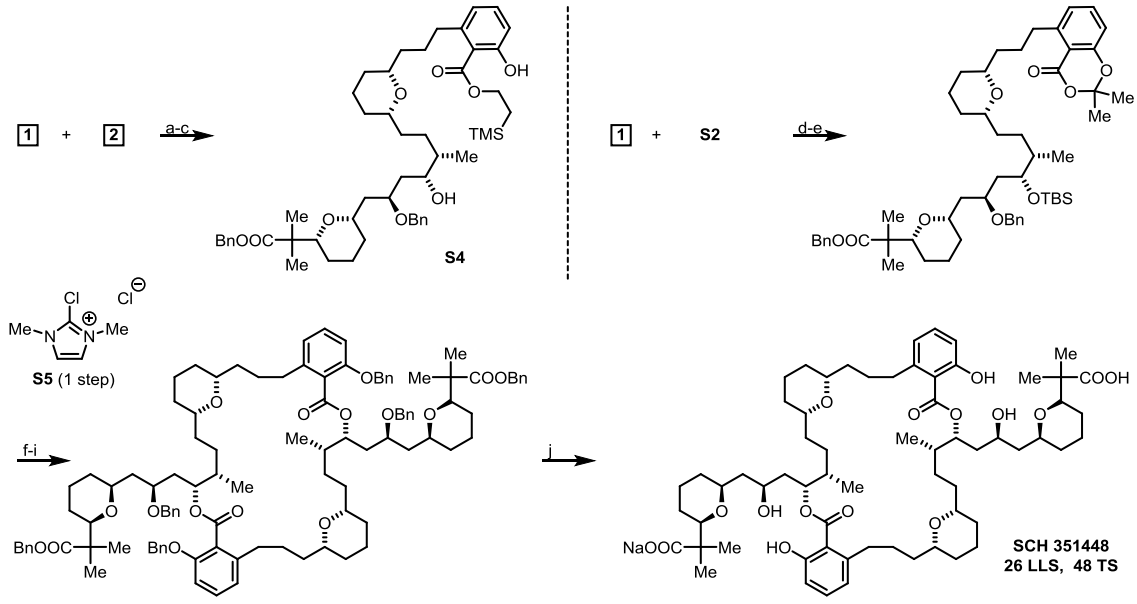
Key: (a) TMSOTf, CH_2Cl_2/PhH (3:1), -78 °C; (b) 10% Pd/C, H_2; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (d) $NaClO_2$-NaH_2PO_4-H_2O, 2-methyl-2-butene, ^{t}BuOH; (e) BnBr, DBU, MeCN; (f) NaCN, DMF, 60 °C; (g) Raney-Ni, NaH_2PO_2, Pyr/HOAc/H_2O (2:1:1), 50 °C; (h) $Ipc_2BAllyl$, THF, -78 °C; (i) BnBr, NaH, DMF, 0 °C; (j) OsO_4, NMO, acetone/H_2O (3:1); (k) $NaIO_4$, THF; (l) ^{t}BuOK, *trans*-2-butene, ^{n}BuLi, $B(^dIpc)_2OMe$, THF, -78 °C; (m) TBSOTf, lutidine.

Fragment 2



Key: (a) 3-Butyn-1-ol, DIPA, $Pd(PPh_3)_2Cl_2$, CuI, dioxane, 85 °C; (b) 10% Pd/C, H_2, MeOH; (c) PCC, CH_2Cl_2; (d) **S1**, TMSOTf, CH_2Cl_2/PhH (3:1), -78 °C; (e) 10% Pd/C, H_2, MeOH; (f) NaI, acetone, reflux; (g) AgOAc, DMF, 100 °C; (h) $Sc(OTf)_3$, MeOH/H_2O (4:1); (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C; (j) **S3**, NaHMDS, THF, -78 °C; (k) 2-(Trimethylsilyl)ethanol, NaHMDS, THF; (l) BnBr, Cs_2CO_3.

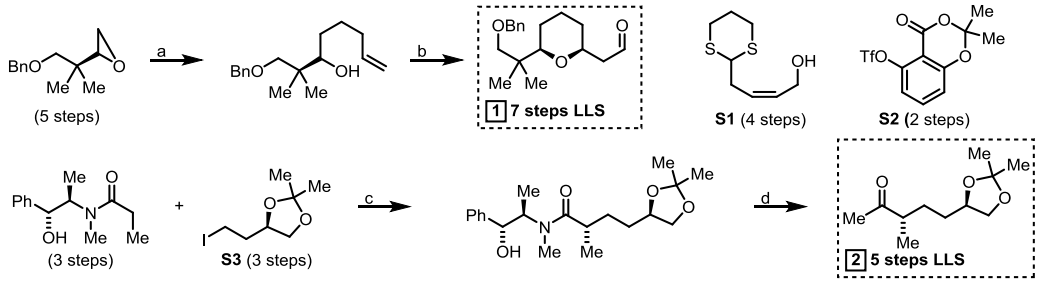
Fragment Union and End Game



Key: (a) Grubbs-Hoveyda II, C_6H_5Cl, 85 °C; (b) *p*-$TsNHNH_2$, NaOAc, DME/H_2O, reflux; (c) HCl, MeOH; (d) Grubbs-Hoveyda II, C_6H_5Cl, 70 °C, 12 h; (e) *p*-$TsNHNH_2$, NaOAc, DME/H_2O (1:1), 100 °C; (f) **S4**, NaHMDS, THF, -78 °C; (g) BnBr, Cs_2CO_3, DMF; (h) TBAF, THF, 0 °C; (i) DMAP, CH_2Cl_2, 42 °C, **S5**; (j) Pd/C, H_2, MeOH, then 4 N HCl in NaCl.

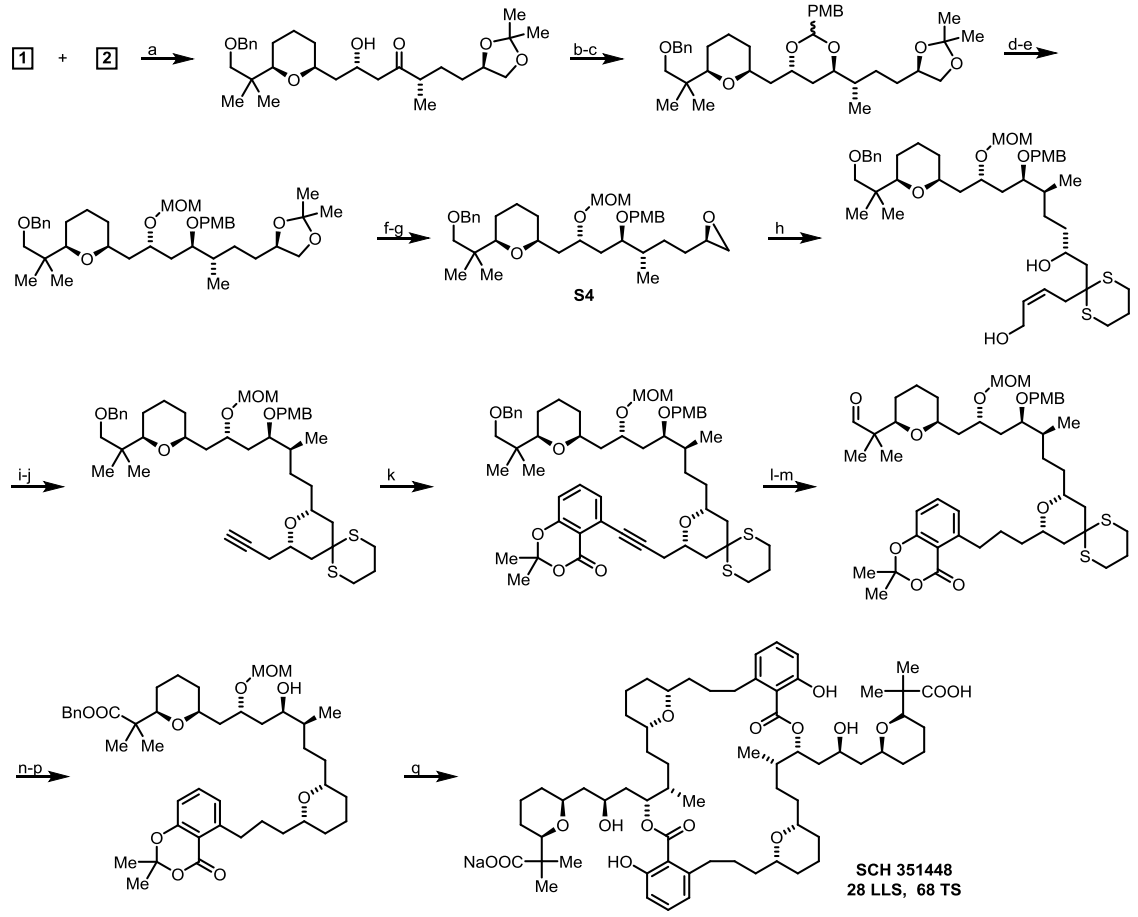
H. Hong *et al. Org. Lett.* **2011**, *13*, 3742.

Fragment 1 and 2



Key: (a) 3-Butenylmagnesium bromide, CuI, THF, -20 °C, 1 h; (b) crotonaldehyde, Hoveyda-Grubbs' II, toluene, 110 °C, 18 h; (c) LDA, LiCl, THF, -78 °C, 1 h, then **S3**, 25 °C, 3 h; (d) CH_3Li, THF, 0 °C, 0.5 h.

Fragment Union and End Game



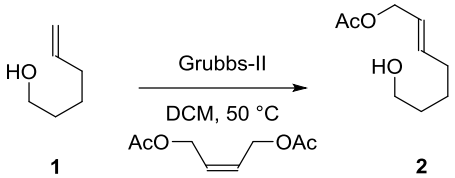
Key: (a) (-)-Ipc$_2$BCl, Et_3N, Et_2O, 0 °C, 1 h, then **1**, -78 °C, 2 h, -20 °C, 16 h; (b) $Me_4NBH(OAc)_3$, CH_3CN/HOAc, 25 °C, 4 h; (c) *p*-anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, 25 °C, 2 h; (d) DIBAL, toluene, -20 °C, 1 h; (e) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 25 °C, 24 h; (f) PPTS, $CHCl_3$/MeOH, 25 °C, 48 h; (g) NaH, 1-tosylimidazole, THF, 25 °C, 6 h; (h) **S1**, ^{t}BuLi, THF/HMPA (4:1), -78 °C, 5 min; then **S4**, -78 °C, 1 h; (i) MnO_2, CH_2Cl_2, 25 °C, 8 h; (j) *p*-TsN_3, K_2CO_3, $(MeO)_2P(O)CH_2COCH_3$, CH_3CN, MeOH, 25 °C, 18 h; (k) **S2**, NaHMDS, B-OMe-9-BBN, KBr, $PdCl_2$(dppf), THF, reflux, 3 h; (l) H_2, Raney-Ni, EtOH, 50 °C, 40 h; (m) Dess-Martin periodinane, pyridine, CH_2Cl_2, 25 °C, 5 h; (n) $NaClO_2$, NaH_2PO_4-H_2O, 2-methyl-2-butene, ^{t}BuOH/H_2O (1/1), 25 °C, 4 h; (o) BnBr, Cs_2CO_3, CH_3CN, 25 °C, 2 h; (p) DDQ, CH_2Cl_2/H_2O, 25 °C, 1 h; (q) De Brabander *et al. Org. Lett.* **2002**, *4*, 481.; *Org. Lett.* **2005**, *7*, 2791.

General Information

All reactions were carried out in oven- or flame-dried flasks, under an inert atmosphere of argon or nitrogen if anhydrous conditions were required. Anhydrous solvents were transferred by oven-dried syringes and needles. Reagents obtained from Acros, Sigma-Aldrich, Alfa Aesar, Fisher Scientific, Takasago, Oakwood, or Strem Fine Chemicals suppliers were used directly as supplied or following purification according to procedures described by Amarego and Chai.[1] Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were distilled prior to use. Thin layer chromatography (TLC) was performed on Dynamic Adsorbents F254 0.25 mm precoated silica gel plates. Compounds were visualised under UV light and by staining with potassium permanganate, or *para*-anisaldehyde solution. Flash column chromatography was performed using silica gel (40–63 μm, Silicycle) and using head pressure by means of a positive pressure from an air line, according to Still.[2] Infra-red spectra were recorded on a Thermo Nicolet 380 spectrometer. High-resolution mass spectra were recorded on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI) and are reported as a ratio of mass to charge (m/z) in Daltons. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}. ^1H NMR spectra were recorded on an Agilent MR (400 MHz), Varian DirectDrive (400 MHz) spectrometer in $CDCl_3$ or CD_2Cl_2 at ambient temperature. Chemical shifts are quoted to two decimal places in parts per million (ppm) with splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). Coupling constants, *J*, are quoted to one decimal place in Hz. ^{13}C NMR spectra were recorded on an Agilent MR (100 MHz), Varian DirectDrive (100 MHz spectrometer in $CDCl_3$ or CD_2Cl_2 with broadband decoupling. Chemical shifts are quoted to one decimal place in parts per million (ppm). All NMR chemical shifts were referenced to residual solvent peaks ($CDCl_3$, δ_H 7.26 ppm, δ_C 77.0 ppm; CD_2Cl_2 δ_H 5.32 ppm, δ_C 53.8 ppm).

Experimental Procedure and Characterization of Intermediates:

(*E*)-7-hydroxyhept-2-en-1-yl acetate (2)



1 2

To a sealed tube under an argon atmosphere charged with hex-5-en-1-ol (**1**) (400.6 mg, 4.0 mmol, 100 mol%) and *cis*-1,4-diacetoxy-2-butene (688.7 mg, 16.0 mmol, 400 mol%) was added freshly distilled CH_2Cl_2 (22 mL, 0.18 M). The Grubbs' second generation catalyst [$Cl_2(PCy_3)(IMes)Ru{=}CHPh$] (101.9 mg, 0.12 mmol, 3 mol%) was added in one portion. The septum was quickly replaced with a screw cap, and the reaction mixture was allowed to stir at 50 ^oC for 20 h. The reaction mixture was allowed to cool ambient temperature, at which point it was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 4:1 to 2:1) to furnish the title product **2** in 87% yield (600 mg, 3.48 mmol, *E:Z*=7:1).

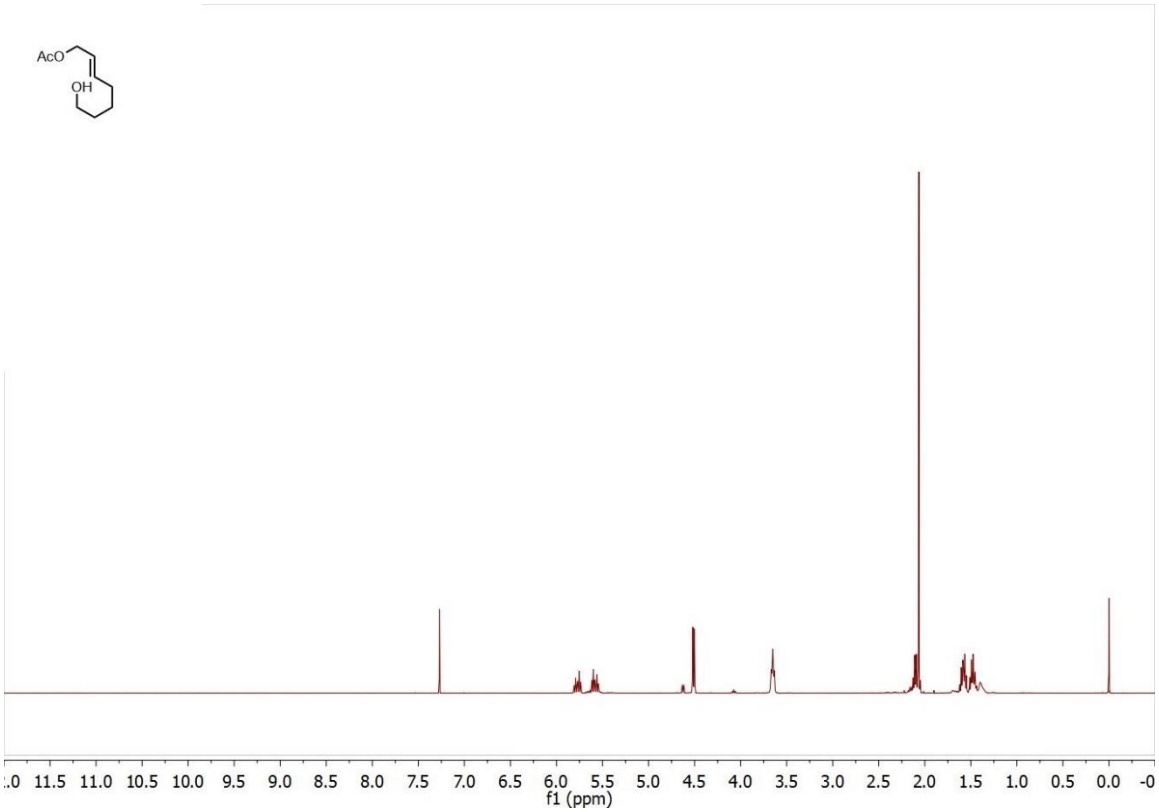
Spectral data is reported for the major isomer.

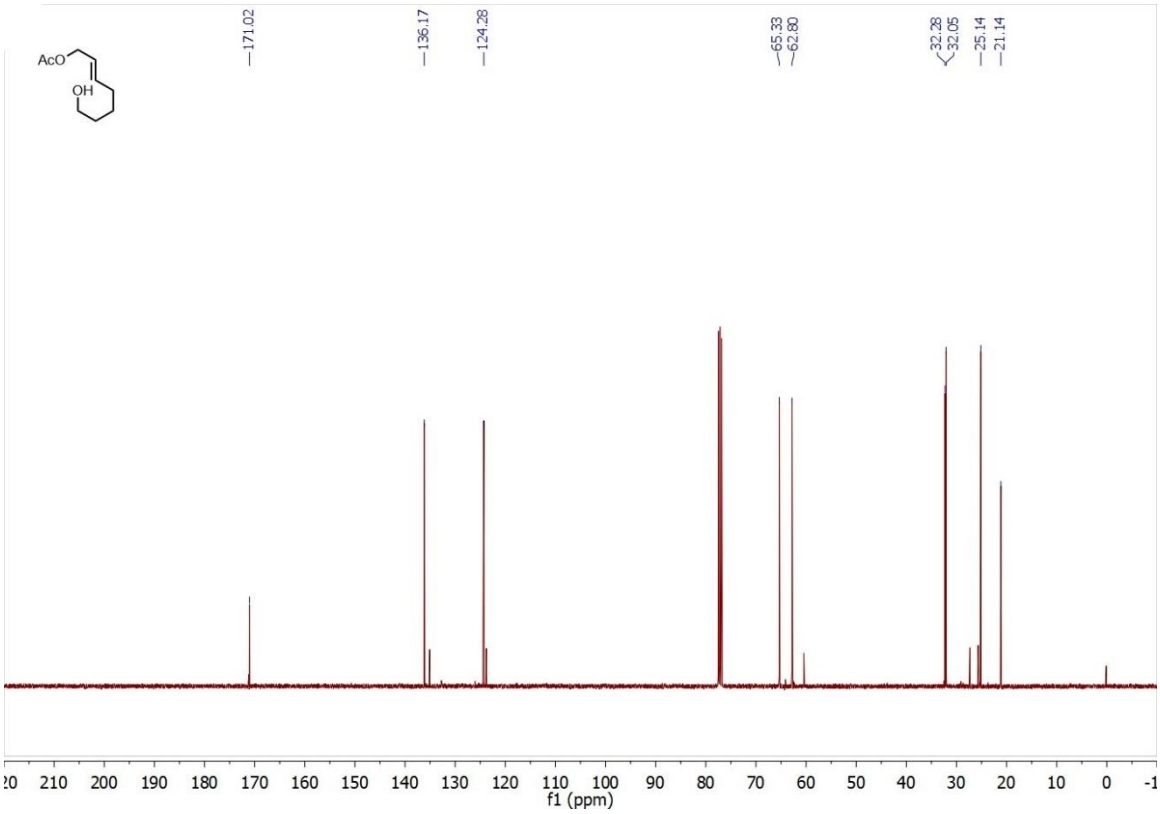
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.71 (m, 1H), 5.58 (dtt, *J* = 15.6, 6.5, 1.4 Hz, 1H), 4.51 (dd, *J* = 6.5, 1.1 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.14–2.07 (m, 2H), 2.06 (s, 3H), 1.64–1.53 (m, 2H), 1.52–1.44 (m, 2H), 1.40 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.2, 124.3, 65.3, 62.8, 32.3, 32.1, 25.1, 21.1.

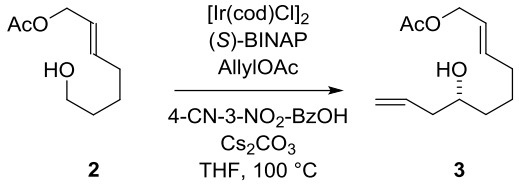
HRMS (ESI) Calcd. for $C_9H_{16}O_3Na$ $[M+Na]^+$: 195.0992, Found: 195.0996.

FTIR (neat): 3381, 2934, 1736, 1364, 1227, 1023, 969 cm^{-1}.


AcO
OH
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


AcO
OH
171.02
136.17
124.28
65.33
62.80
32.28
32.05
25.14
21.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*R*,*E*)-7-hydroxydeca-2, 9-dien-1-yl acetate (3)



2 **3**

To a sealed tube under an argon atmosphere charged with alcohol **2** (390.0 mg, 2.27 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (38.3 mg, 0.057mmol, 2.5 mol%), (*S*)-BINAP (71.0 mg, 0.114 mmol, 5.0 mol%), Cs_2CO_3 (148.0 mg, 0.45 mmol, 20 mol%) and 4-CN-3-NO_2-BzOH (39.3 mg, 0.23 mmol, 10 mol%) was added freshly distilled THF (11.4 mL, 0.2 M) and allyl acetate (454.5 mg, 4.54 mmol, 200 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir at 100 °C for 72 h. The reaction mixture was allowed to cool to ambient temperature, at which point it was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 8:1 to 4:1) to furnish the title product **3** in 62% yield (298.8 mg, 1.41 mmol, 96% *ee*), catalyst was recovered using DCM/ether, 4:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.73 (m, 2H), 5.58 (dtt, *J* = 15.4, 6.6, 1.4 Hz, 1H), 5.23–5.09 (m, 2H), 4.51 (dt, *J* = 6.5, 1.0 Hz, 2H), 3.72–3.61 (m, 1H), 2.31 (dddt, *J* = 13.7, 6.2, 4.2, 1.3 Hz, 1H), 2.19–2.07 (m, 3H), 2.06 (s, 3H), 1.71 (br s, 1H), 1.63–1.53 (m, 1H), 1.53–1.43 (m, 3H).

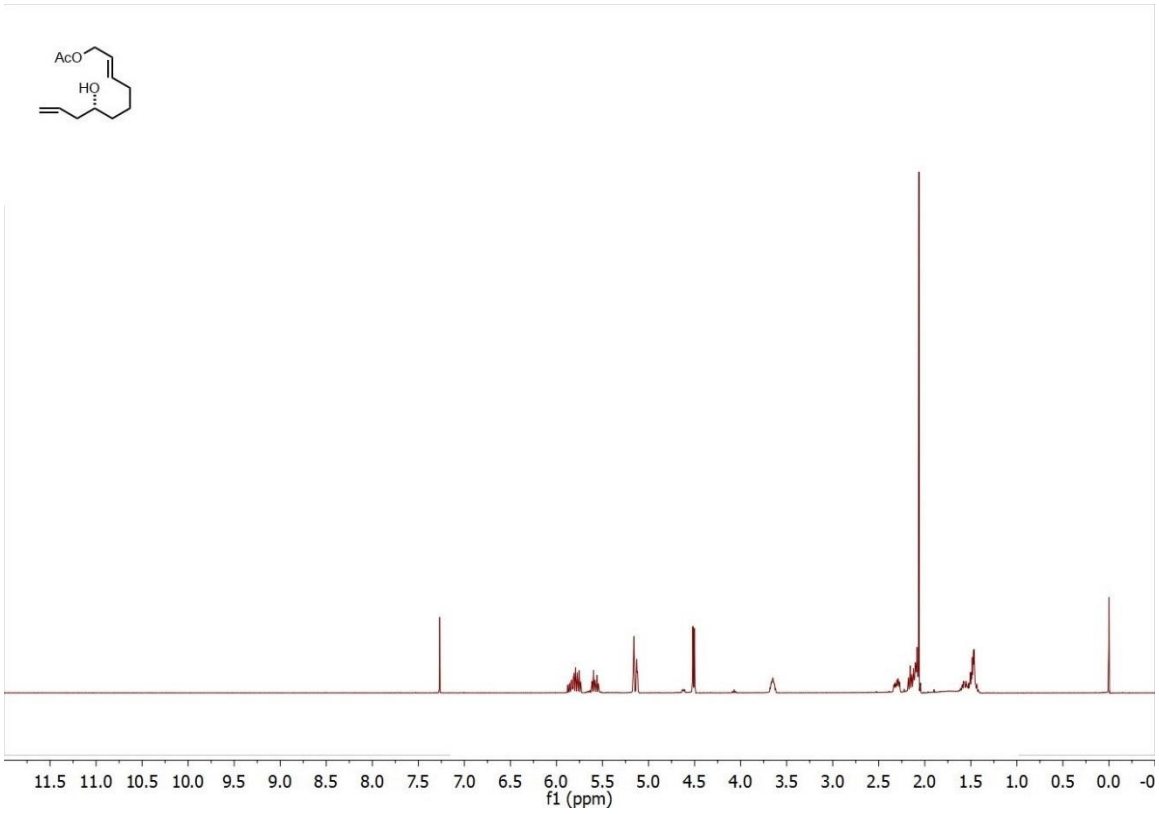
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.3, 134.9, 124.3, 118.4, 70.6, 65.4, 42.1, 36.3, 32.3, 25.1, 21.2.

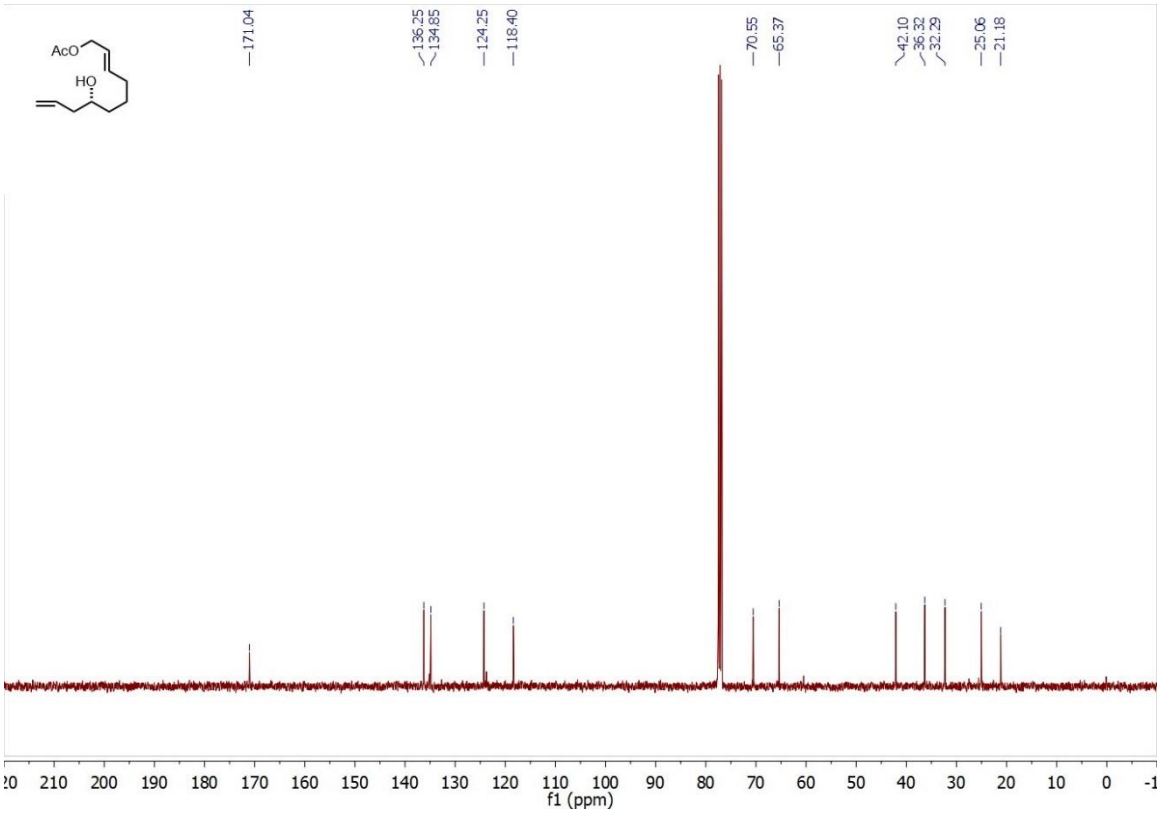
HRMS (ESI) Calcd. for $C_{12}H_{20}O_3Na$ $[M+Na]^+$: 235.1305, Found: 235.1309.

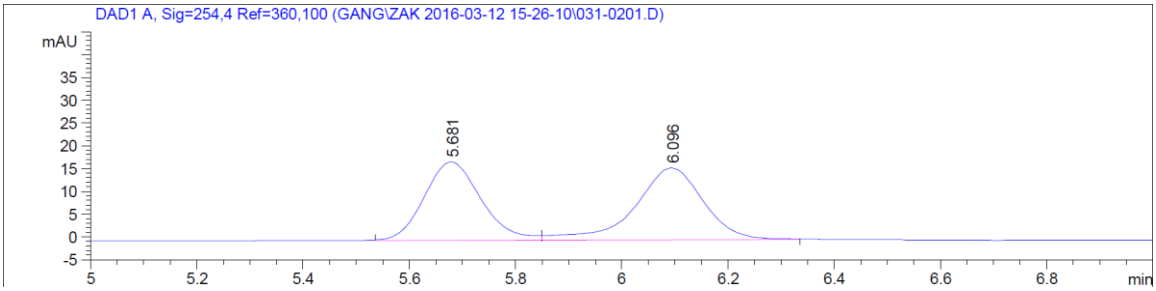
FTIR (neat): 3420, 2933, 1738, 1437, 1363, 1231, 1024, 969, 913 cm^{-1}.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =96% (Alcohol **3** was protected with benzyl group).

$[\alpha]^{20}_D$ = +10.00 ° (c 1.0, $CHCl_3$).

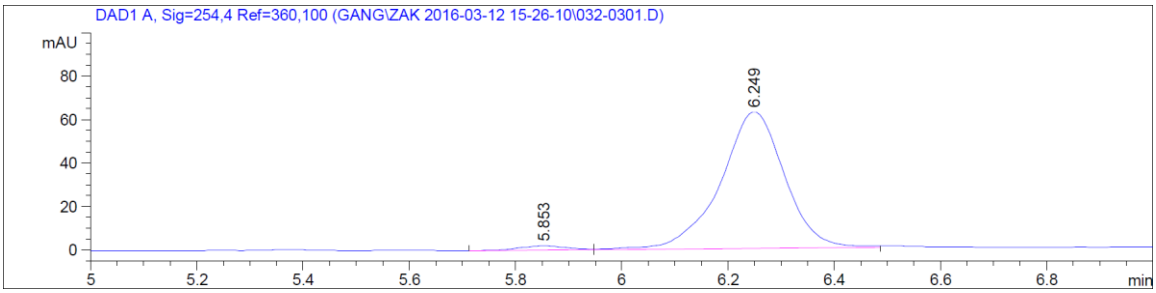

AcO
HO
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


AcO
HO
171.04
136.25
134.85
124.25
118.40
70.55
65.37
42.10
36.32
32.29
25.06
21.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

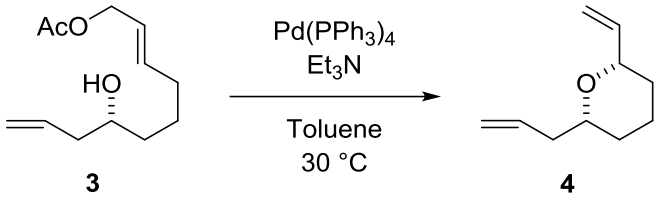
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.681	BV	0.1143	126.99027	17.17166	47.3036
2	6.096	VB	0.1347	141.46756	15.76023	52.6964
Totals :				268.45783	32.93188	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.853	BV	0.0964	11.10787	1.83955	2.0613
2	6.249	VB	0.1258	527.78131	62.97322	97.9387
Totals :				538.88918	64.81277	

(2*R*,6*S*)-2-allyl-6-vinyltetrahydro-2*H*-pyran (4)



To a sealed tube under an argon atmosphere charged with $Pd(PPh_3)_4$ (208.0 mg, 0.18 mmol, 18 mol%) and toluene (8.30 mL) was added Et_3N (202.4 mg, 2.0 mmol, 200 mol%). Alcohol **3** in toluene (4.2 mL) was added to the reaction mixture. The reaction mixture was allowed to stir for at 30 °C for 48 h. The reaction mixture was directly subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 100:0 to 25:1) to furnish the title product **4** in 65% yield (98.9 mg, 0.65 mmol, 6:1 *dr*).

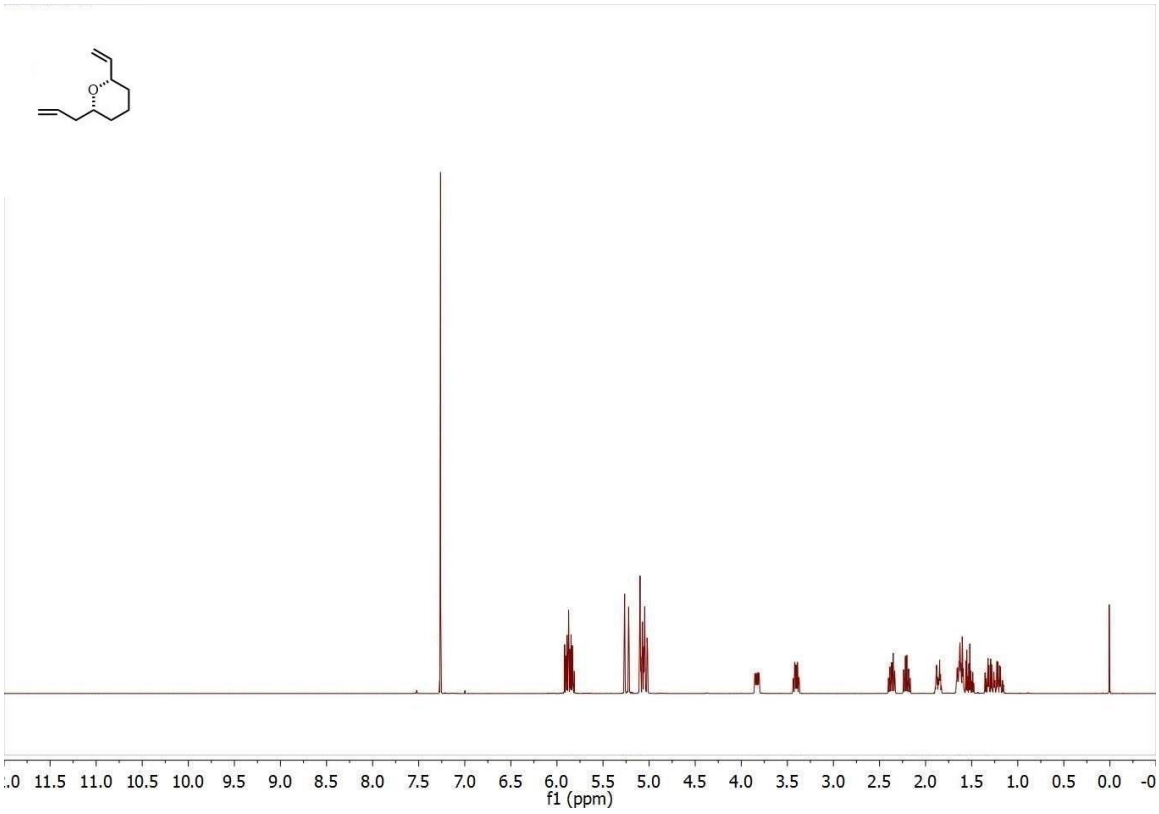
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.79 (m, 2H), 5.24 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.13–4.99 (m, 3H), 3.83 (dddd, *J* = 10.7, 5.3, 2.6, 1.5 Hz, 1H), 3.40 (dtd, *J* = 11.2, 6.3, 2.0 Hz, 1H), 2.37 (dtt, *J* = 14.3, 6.5, 1.5 Hz, 1H), 2.20 (dddt, *J* = 14.0, 7.6, 6.4, 1.2 Hz, 1H), 1.92–1.80 (m, 1H), 1.70–1.57 (m, 2H), 1.52 (tt, *J* = 13.0, 3.9 Hz, 1H), 1.37–1.14 (m, 2H).

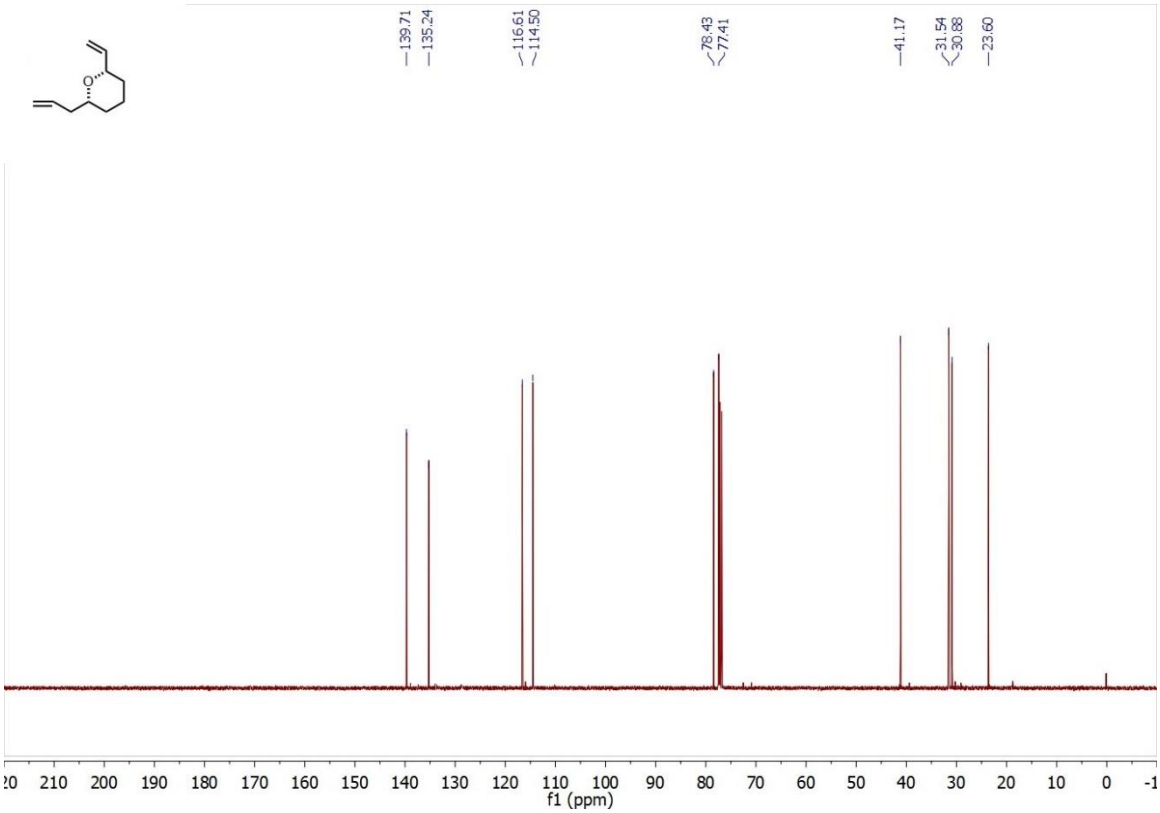
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 135.2, 116.6, 114.5, 78.4, 77.4, 41.2, 31.5, 30.9, 23.6.

HRMS (CI) Calcd. for $C_{10}H_{17}O$ $[M+H]^+$: 153.1279, Found: 153.1278.

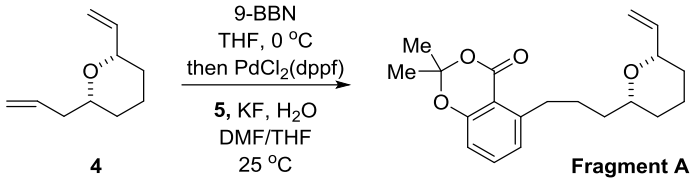
FTIR (neat): 3075, 2935, 2844, 1642, 1434, 1200, 1083, 1046, 994, 914, 696 cm^{-1}.

$[\alpha]^{20}_D$ = -4.70 ° (c 1.0, $CHCl_3$).


f1 (ppm)


139.71
135.24
116.61
114.50
78.43
77.41
41.17
31.54
30.88
23.60
f1 (ppm)

2,2-dimethyl-5-(3-((2*S*,6*S*)-6-vinyltetrahydro-2*H*-pyran-2-yl)propyl)-4*H*-benzo[d][1,3]dioxin-4-one (Fragment A)



A flask was charged with diene **4** (343.0 mg, 2.25 mmol, 100 mol%) and 2.25 mL (1 M) fresh distilled THF. The flask was cooled to 0 °C for 5 min. 9-BBN (5.86 mL, 2.93 mmol, 130 mol%) was added dropwise over 1h. The reaction mixture was stirred at 0 °C for 0.5 h, and then gradually warmed to ambient temperature. After 4 h, KF (784.0 mg, 13.5 mmol, 600 mol%), 2,2-dimethyl-4-oxo-4*H*-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (**5**)[3] (1100.0 mg, 3.375 mmol, 150 mol%), $PdCl_2$(dppf) (82.7 mg, 0.11 mmol, 5 mol%) and H_2O (486.0 mg, 27.0 mmol, 1200 mol%) in 9.0 mL DMF was added to the reaction mixture. The resulting solution was stirred at ambient temperature for 16 h. EtOAc and H_2O (25 mL : 25 mL) were added to the reaction mixture. The organic layer was washed three times with H_2O (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 50:1 to 25:1) to furnish the title compound **Fragment A** in 55% yield (409.0 mg, 1.24 mmol) along with a 21% yield of recovered diene **4** (72.0 mg, 0.47 mmol).

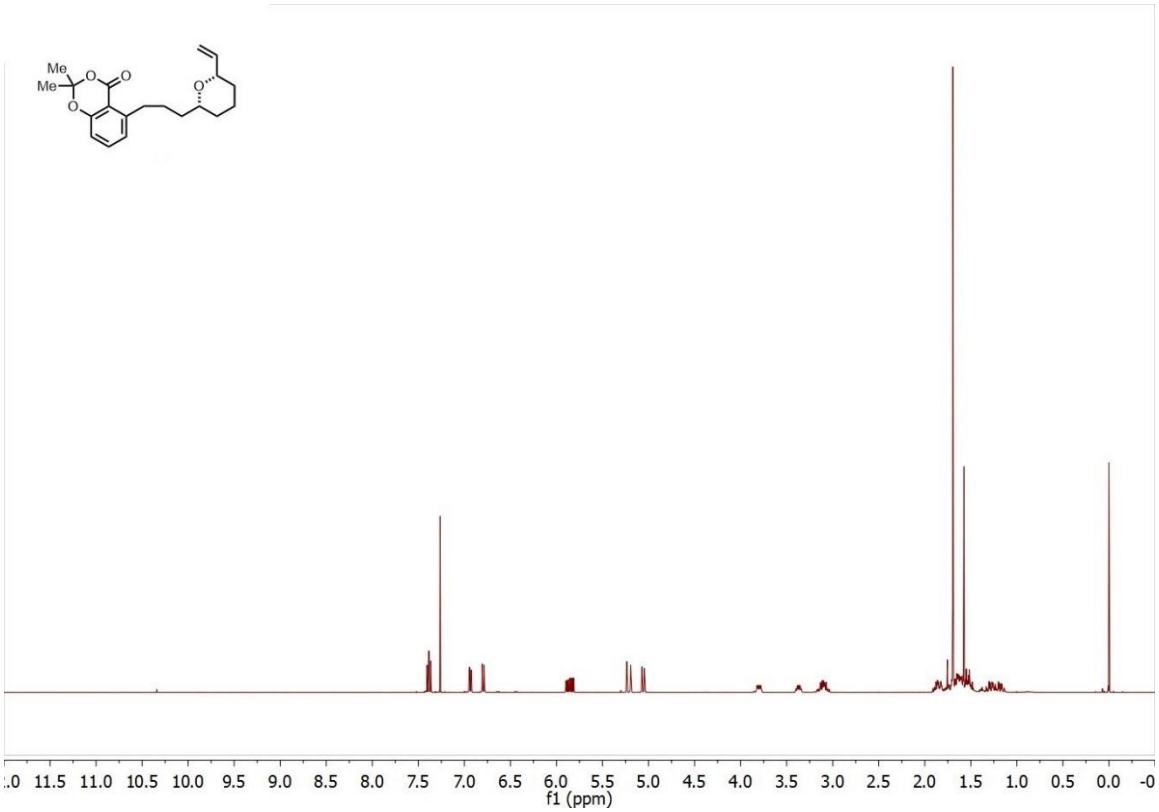
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.2, 7.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.85 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.22 (dt, *J* = 17.4, 1.7 Hz, 1H), 5.06 (dt, *J* = 10.6, 1.6 Hz, 1H), 3.84–3.76 (m, 1H), 3.41–3.33 (m, 1H), 3.17–3.03 (m, 2H), 1.92–1.80 (m, 1H), 1.79–1.45 (m, 13H), 1.34–1.13 (m, 2H).

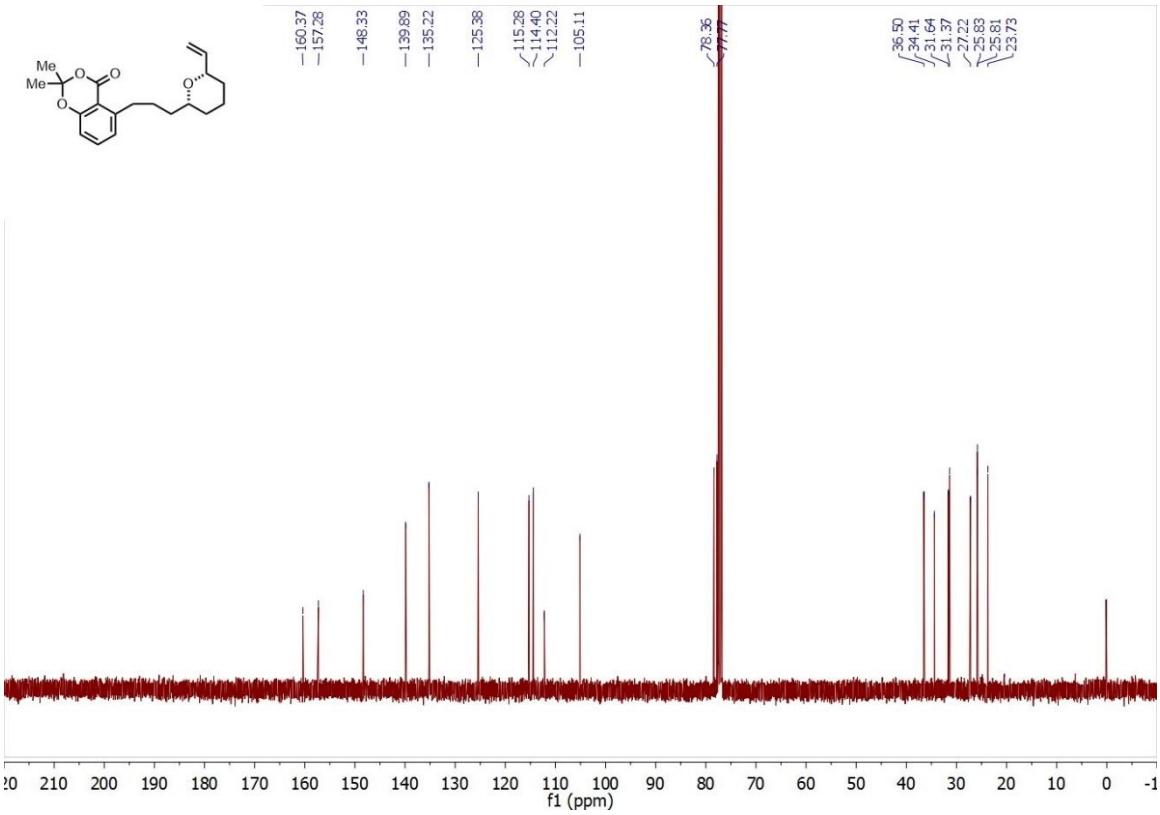
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 157.3, 148.3, 139.9, 135.2, 125.4, 115.3, 114.4, 112.2, 105.1, 78.4, 77.8, 36.5, 34.4, 31.6, 31.4, 27.2, 25.8, 25.8, 23.7.

HRMS (ESI) Calcd. for $C_{20}H_{26}O_4Na$ $[M+Na]^+$: 353.1723, Found: 353.1729.

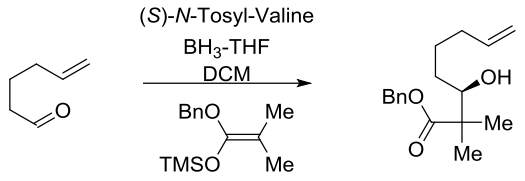
FTIR (neat): 2992, 2932, 2858, 1736, 1695, 1605, 1582, 1476, 1389, 1378, 1313, 1269, 1208, 1074, 1043, 923, 808, 777, 698 cm^{-1}.

$[\alpha]^{20}_D$ = -12.67 ° (c 0.5, $CHCl_3$).


Me
Me
O
O
O
O
f1 (ppm)


160.37
157.28
148.33
139.89
135.22
125.38
115.28
114.40
112.22
105.11
78.36
77.77
36.50
34.41
31.64
31.37
27.22
25.83
25.81
23.73
Me
Me
O
O
O
O
f1 (ppm)

Benzyl (*R*)-3-hydroxy-2,2-dimethyloct-7-enoate (7)



7

BH_3·THF (1.0 M in THF, 11.0 mL, 11.0 mmol) was added dropwise to *N*-tosyl-L-valine[3] (1 step, 2984.3 mg, 11.0 mmol, 100 mol%) in DCM (0.1 M, 110.0 mL) at room temperature over 30 min. Then a solution of 5-hexenal[4] (1 step, 1080.0 mg, 11.0 mmol, 100 mol%) in DCM (11.0 mL) and ((1-(benzyloxy)-2-methylprop-1-en-1-yl)oxy)trimethylsilane[5] (1 step, 3055.0 mg, 12.2 mmol, 110 mol%) were added to the resulting solution at -78 °C. After stirring for 4 h, the reaction was quenched at -78 °C by addition of a pH 7.0 buffer solution (115 mL). The resulting mixture was extracted with DCM (3 X 77.0 mL), and the combined organic extracts were washed with brine (150 mL) and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title product **7** in 70% yield (2128.0 mg, 7.7 mmol, 93% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.14 (s, 2H), 5.03–4.91 (m, 2H), 3.63 (ddd, *J* = 10.4, 6.9, 1.8 Hz, 1H), 2.37–2.34 (m, 1H), 2.04 (dtt, *J* = 13.3, 6.8, 1.4 Hz, 2H), 1.73–1.64 (m, 1H), 1.47–1.34 (m, 2H), 1.31–1.22 (m, 1H), 1.20 (d, *J* = 2.4 Hz, 6H).

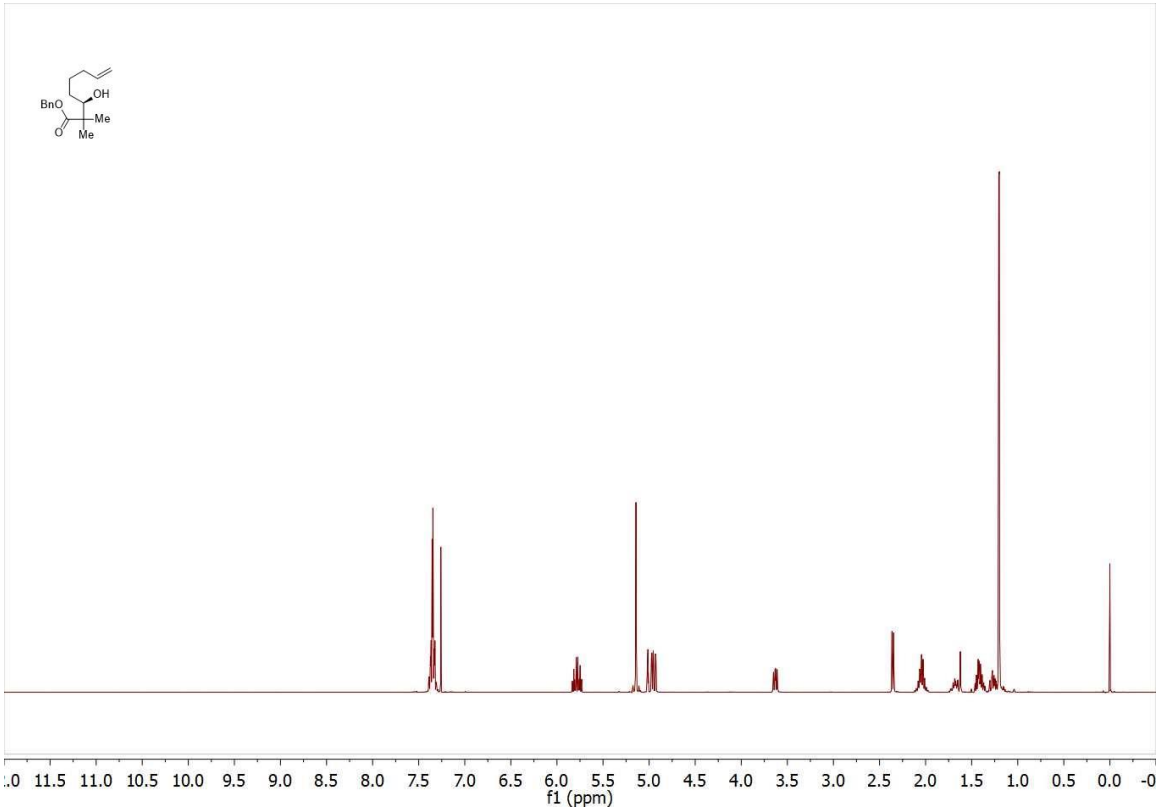
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 138.6, 135.9, 128.6, 128.2, 127.9, 114.6, 76.5, 66.3, 47.3, 33.5, 31.1, 25.9, 22.2, 20.4.

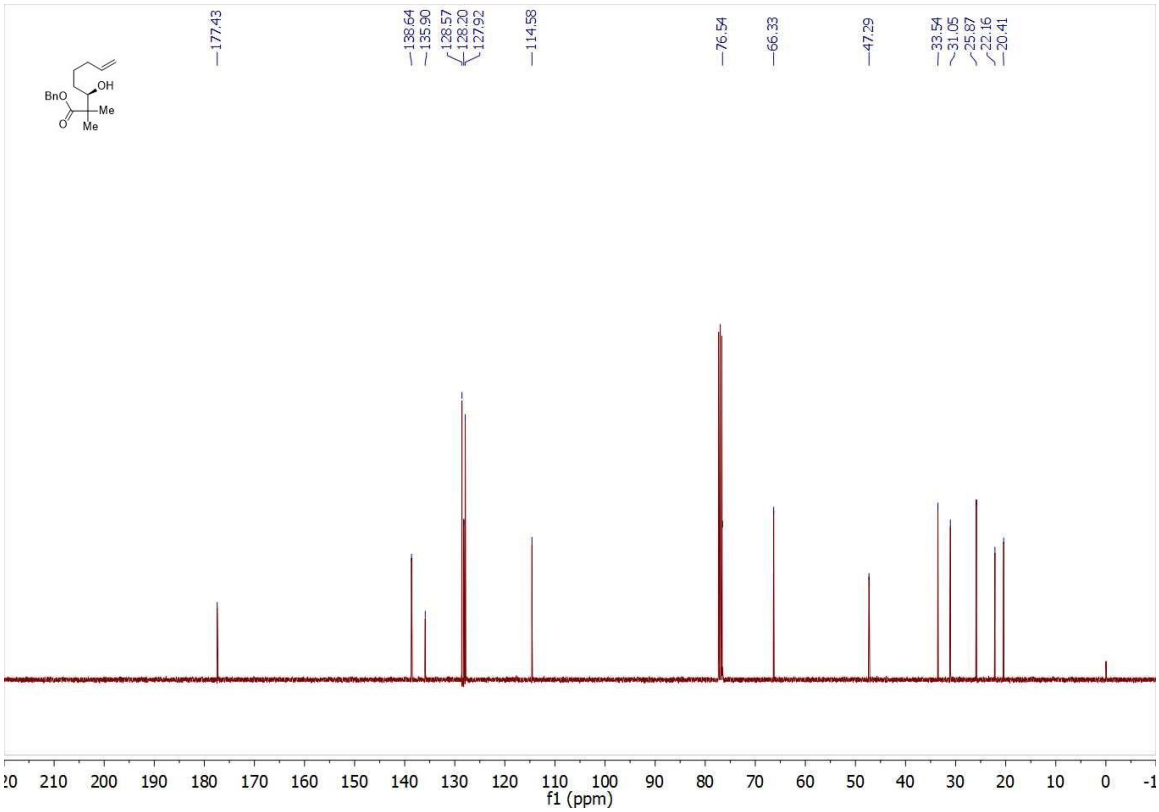
HRMS (ESI) Calcd. for $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1618, Found: 299.1619.

FTIR (neat): 3504, 2976, 2937, 1720, 1455, 1390, 1263, 1213, 1133, 1078, 1029, 993, 969, 911, 750, 697 cm^{-1}.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.00 mL/min, 254 nm), *ee* =93%.

$[\alpha]^{20}_D$ = +11.11 ° (c 0.9, $CHCl_3$).


BnO
OH
Me
Me
O
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


177.43
138.64
135.90
128.57
128.20
127.92
114.58
76.54
66.33
47.29
33.54
31.05
25.87
22.16
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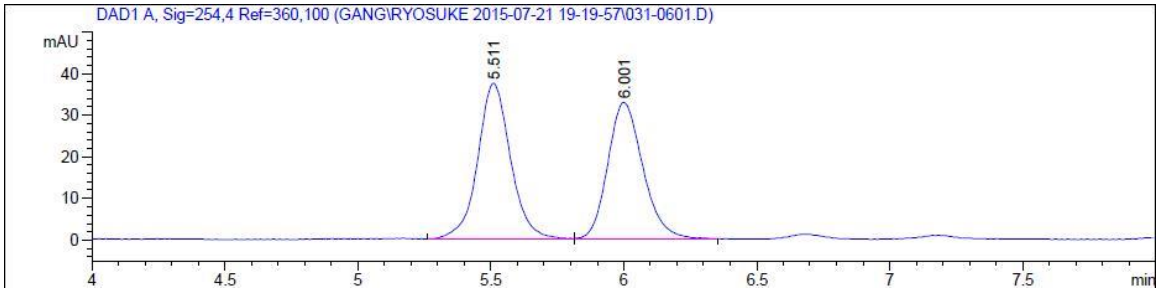
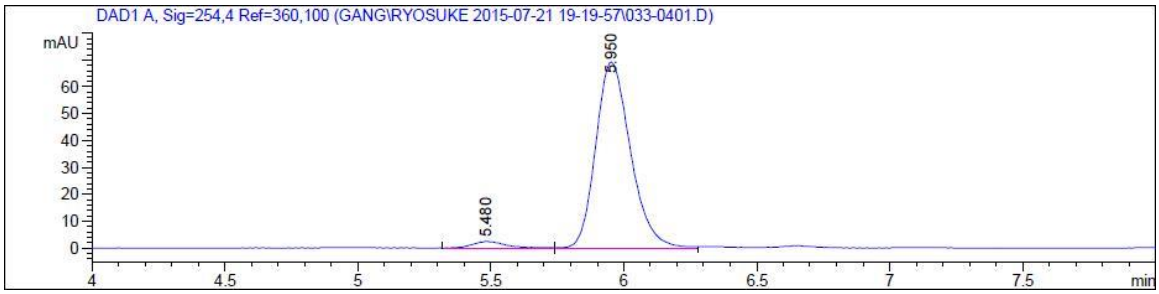
BnO
OH
Me
Me
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

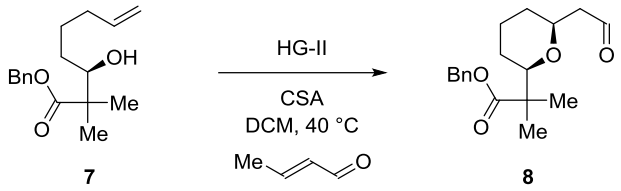
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.511	BV	0.1334	326.93433	37.60009	51.5288
2	6.001	VB	0.1406	307.53488	33.03806	48.4712
Totals :				634.46921	70.63815	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.480	VV	0.1149	22.31137	2.53014	3.4254
2	5.950	VV	0.1401	629.04224	69.19113	96.5746
Totals :				651.35360	71.72127	

Benzyl 2-methyl-2-((2*R*,6*S*)-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl)propanoate (8)



A flame dried flask was charged Hoveyda-Grubbs' 2nd catalyst (551.4 mg, 0.88 mmol, 10 mol%) and (*S*)-camphorsulfonic acid (204.3 mg, 0.88 mmol, 10 mol%). The flask was sealed with a septum and purged with Ar, then freshly distilled CH_2Cl_2 (0.2 M, 44 mL) was added. Alcohol **7** (2432 mg, 8.8 mmol, 100 mol%) and crotonaldehyde (2467 mg, 35.2 mmol, 400 mol%) were added. The resulting mixture was stirred at 35 °C for 10 h. The crude mixture was cooled down to ambient temperature, concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title product **8** in 85% yield (2277.0 mg, 7.48 mmol, >20:1 *dr*).

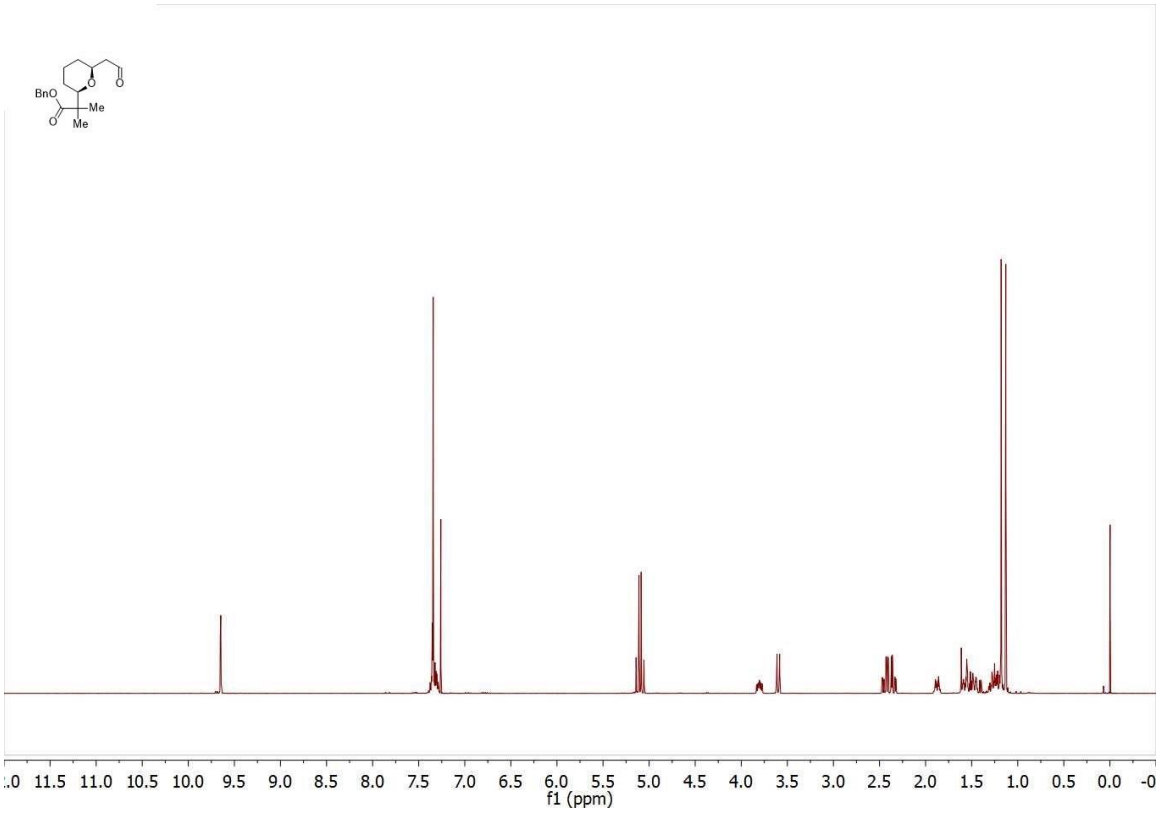
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (dd, *J* = 2.7, 2.0 Hz, 1H), 7.40–7.26 (m, 5H), 5.13 (d, *J* = 12.6 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 3.84–3.76 (m, 1H), 3.60 (dd, *J* = 11.4, 1.9 Hz, 1H), 2.48–2.31 (m, 2H), 1.92–1.83 (m, 1H), 1.60–1.43 (m, 3H), 1.32–1.19 (m, 2H), 1.18 (s, 3H), 1.13 (s, 3H).

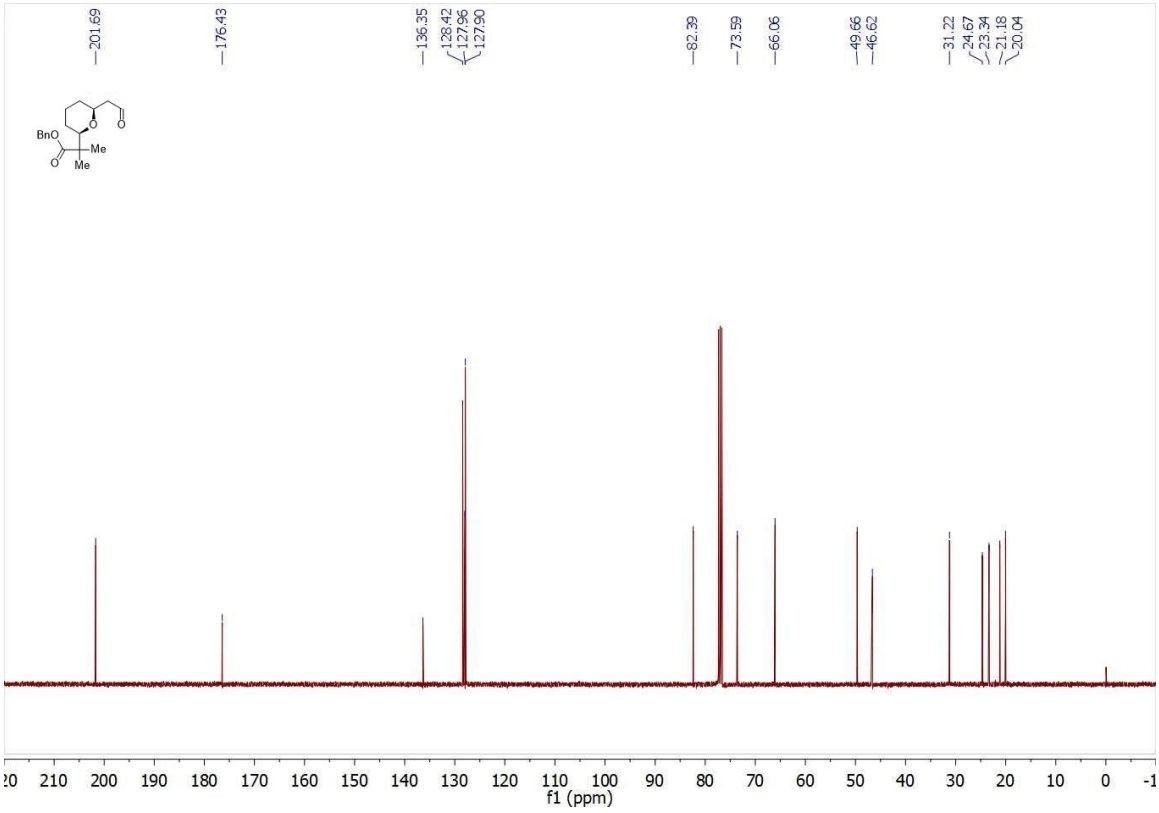
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 176.4, 136.4, 128.4, 128.0, 127.9, 82.4, 73.6, 66.1, 49.7, 46.6, 31.2, 24.7, 23.3, 21.2, 20.0.

HRMS (ESI) Calcd. for $C_{18}H_{24}O_4Na$ $[M+Na]^+$: 327.1567, Found: 327.1576.

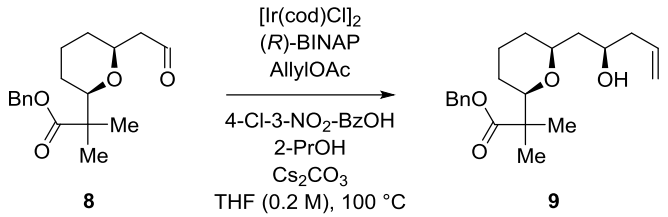
FTIR (neat): 2940, 2860,1727, 1497, 1455, 1391, 1265, 1134, 1085, 1048, 976, 749, 697 cm^{-1}.

$[\alpha]^{20}_D$ = -3.30° (c 1.0, $CHCl_3$).


BnO
Me
Me
f1 (ppm)


201.69
176.43
136.35
128.42
127.96
127.90
82.39
73.59
66.06
49.66
46.62
31.22
24.67
23.34
21.18
20.04
BnO
Me
Me
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*R*)-2-hydroxypent-4-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (9)



To a sealed tube under an argon atmosphere charged with aldehyde **8** (304.4 mg, 1.00 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol, 2.5 mol%), (*R*)-BINAP (31.1 mg, 0.05 mmol, 5.0 mol%), 2-propoanol (180.3 mg, 3.00 mmol, 300 mol%), Cs_2CO_3 (65.1 mg, 0.20 mmol, 20 mol%) and 4-Cl-3-NO_2-BzOH (20.16 mg, 0.10 mmol, 10 mol%) was added freshly distilled THF (5.0 mL, 0.2 M) and allyl acetate (200.2 mg, 2.00 mmol, 200 mol%). The reaction mixture was allowed to stir in a microwave reactor at 100 °C for 6 h. The reaction mixture was allowed to cool to ambient temperature, at which point it was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 15:1 to 8:1) to furnish the title product **9** in 82% yield (284.1 mg, 0.82 mmol, >20:1 *dr*).

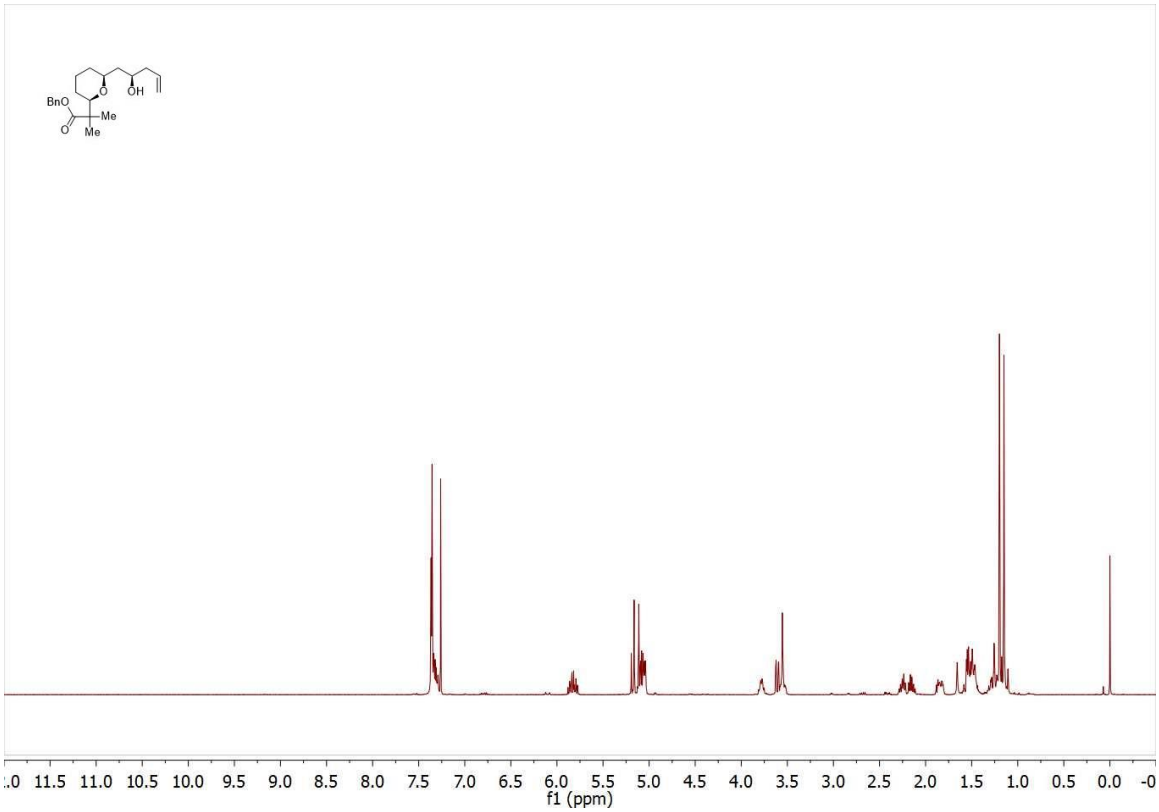
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.83 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.21–5.02 (m, 4H), 3.82–3.74 (m, 1H), 3.61 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.58–3.51 (m, 2H), 2.30–2.21 (m, 1H), 2.19–2.11 (m, 1H), 1.89–1.79 (m, 1H), 1.60–1.43 (m, 5H), 1.33–1.21 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H).

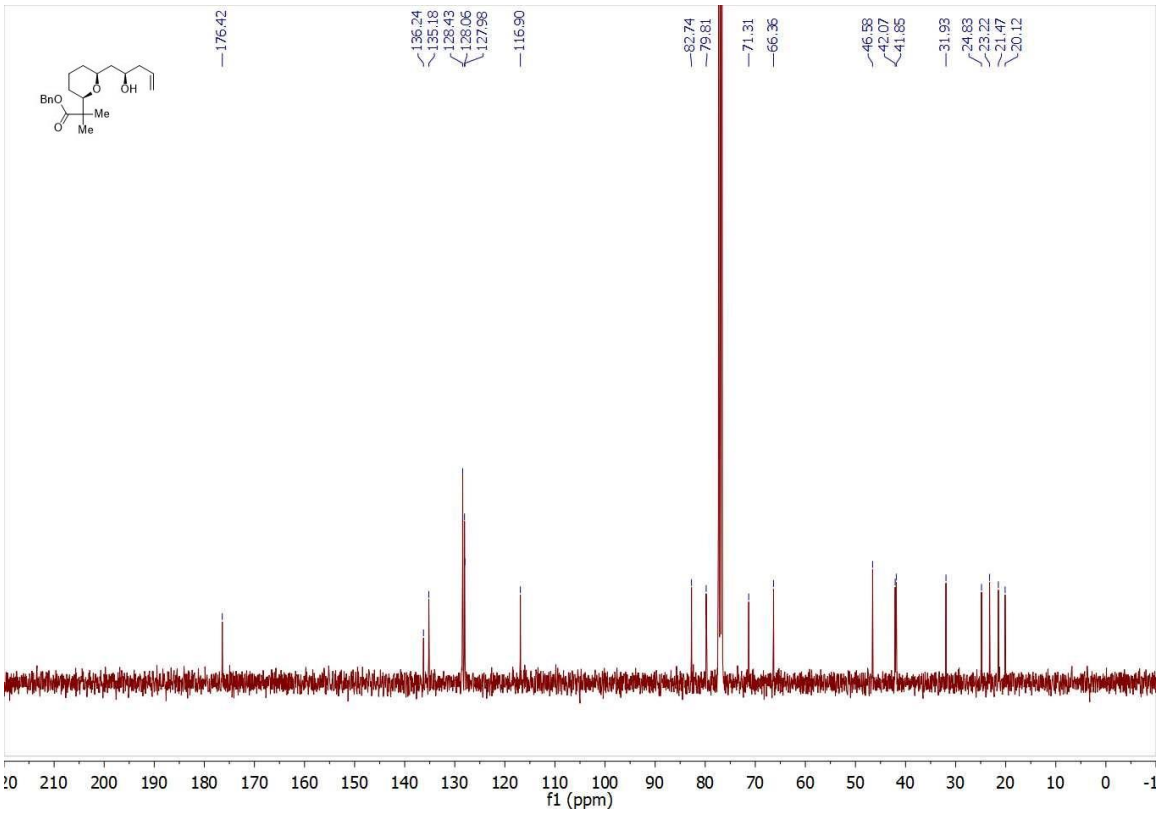
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 136.2, 135.2, 128.4, 128.1, 128.0, 116.9, 82.7, 79.8, 71.3, 66.4, 46.6, 42.1, 41.9, 31.9, 24.8, 23.2, 21.5, 20.1.

HRMS (ESI) Calcd. for $C_{21}H_{30}O_4Na$ $[M+Na]^+$: 369.2036, Found: 369.2043.

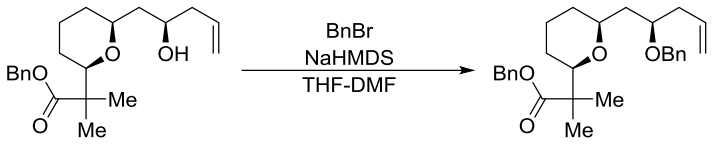
FTIR (neat): 2936, 2860, 1730, 1639, 1455, 1392, 1262, 1140, 1084, 1045, 914, 750, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +2.00° (c 1.0, $CHCl_3$).


BnO
O
Me
Me
OH
.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


176.42
136.24
135.18
128.43
128.06
127.98
116.90
82.74
79.81
71.31
66.36
46.58
42.07
41.85
31.93
24.83
23.22
21.47
20.12
BnO
O
Me
Me
OH
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*R*)-2-(benzyloxy)pent-4-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate



9

A flame dried flask was charged with alcohol **9** (2.22 g, 6.41 mmol, 100 mol%) in THF (74.0 mL) and DMF (18.5 mL) at 0 °C. BnBr (1.64 g, 9.62 mmol, 150 mol%) was added to the solution followed by NaHMDS (1.0 M in THF, 10.3 mL, 10.3 mmol, 160 mol%) at 0 °C. The reaction mixture was warmed to room temperature. After 12 h, aqueous HCl (1 N, 100 mL) was added to the reaction mixture, and the aqueous layer was extracted with ether (3 X 100 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 60:1 to 30:1) to furnish the title compound in 90% yield (2.52 g, 5.77 mmol).

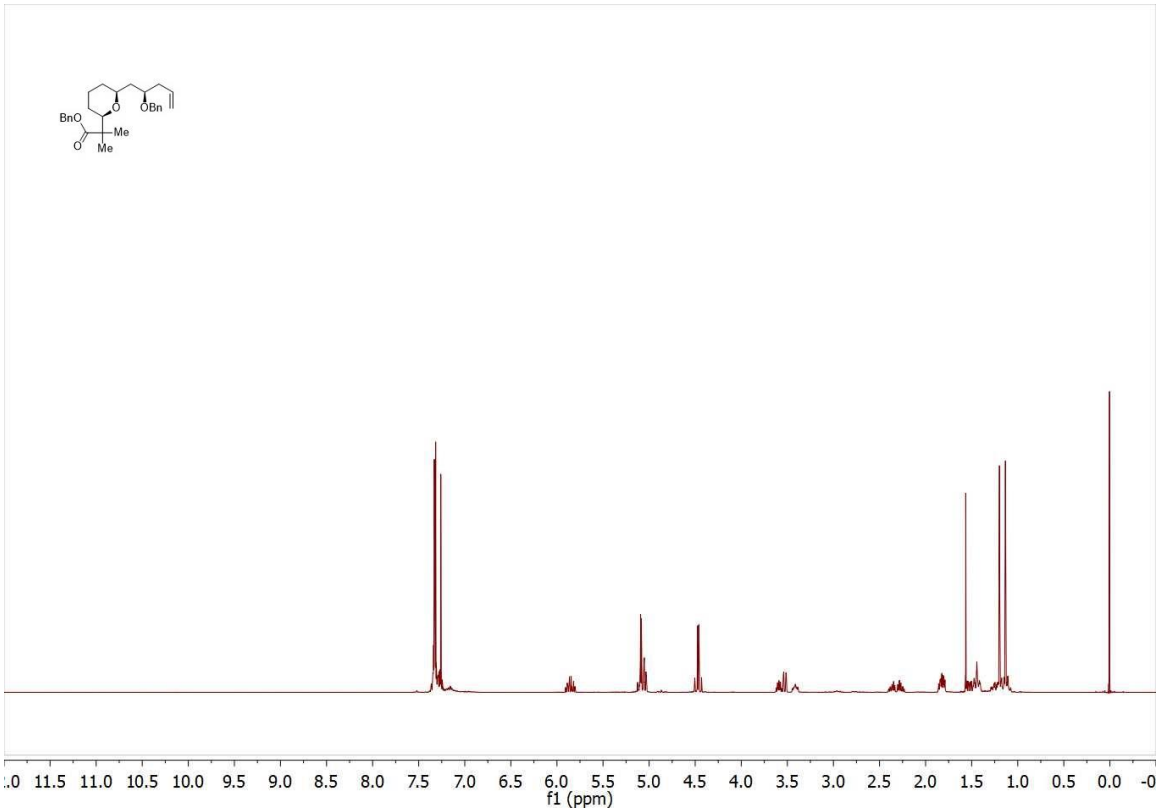
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.13–5.02 (m, 4H), 4.47 (dd, *J* = 11.7 Hz, 2H), 3.62–3.56 (m, 1H), 3.53 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.45–3.38 (m, 1H), 2.41–2.32 (m, 1H), 2.31–2.22 (m, 1H), 1.88–1.77 (m, 2H), 1.58–1.50 (m, 1H), 1.49–1.39 (m, 3H), 1.30–1.21 (m, 2H), 1.20 (s, 3H), 1.13 (s, 3H).

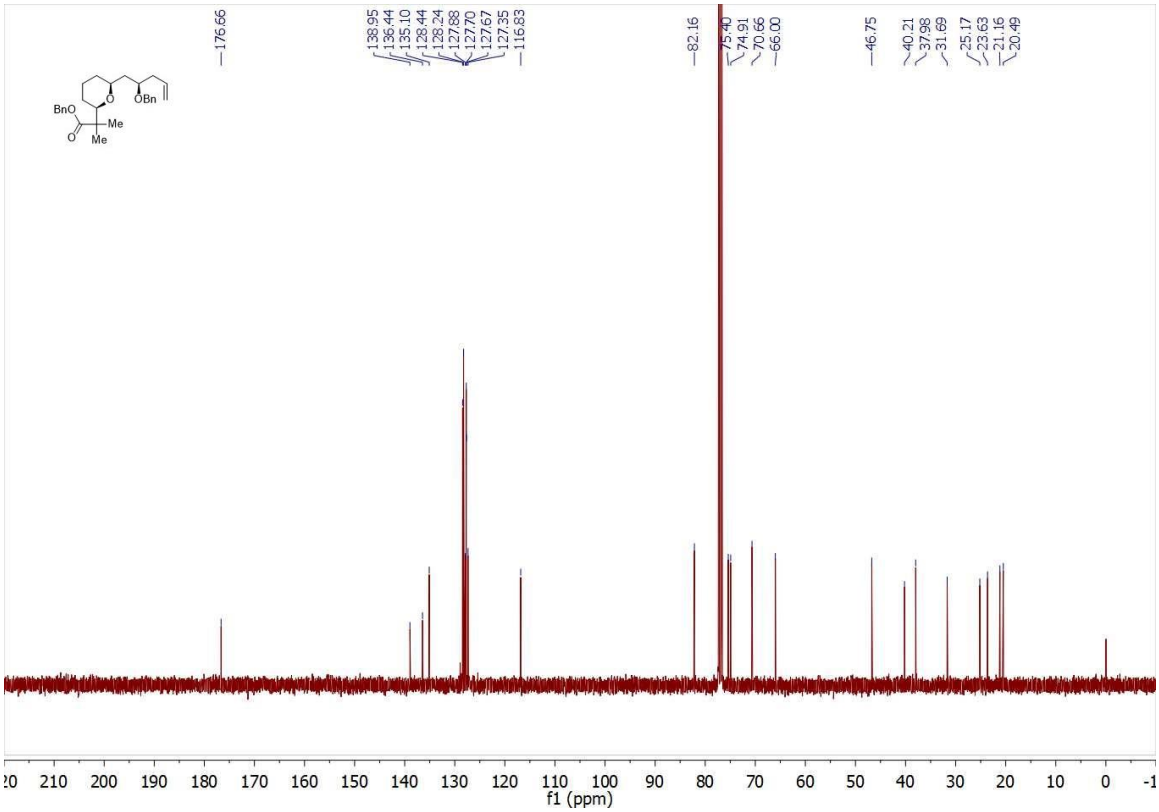
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 138.9, 136.4, 135.1, 128.4, 128.2, 127.9, 127.7, 127.7, 127.4, 116.8, 82.2, 75.4, 74.9, 70.7, 66.0, 46.8, 40.2, 38.0, 31.7, 25.2, 23.6, 21.2, 20.5.

HRMS (ESI) Calcd. for $C_{28}H_{36}O_4Na$ $[M+Na]^+$: 459.2506, Found: 459.2511.

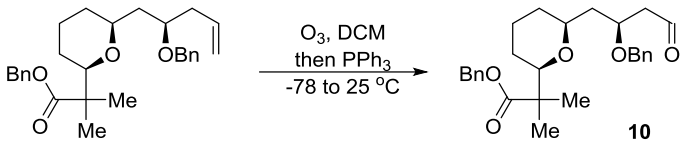
FTIR (neat): 2931, 2858, 2322, 1731, 1640, 1454, 1264, 1134, 1088, 1047, 911, 796, 735, 696, 669 cm^{-1}.

$[\alpha]^{20}_D$ = -20.00° (c 0.4, $CHCl_3$).


BnO
OBn
Me
Me
f1 (ppm)


176.66
138.95
136.44
135.10
128.44
128.24
127.88
127.70
127.67
127.35
116.83
82.16
75.40
74.91
70.66
66.00
46.75
40.21
37.98
31.69
25.17
23.63
21.16
20.49
BnO
OBn
Me
Me
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*S*)-2-(benzyloxy)-4-oxobutyl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (10)



A flask was charged with alkene (2.31 g, 5.29 mmol, 100 mol%) and freshly distilled DCM (88.2 mL, 0.06 M) was added at -78 °C. Ozone was bubbled through the solution for about 15 min at -78 °C. Argon was bubbled through the solution to remove the ozone, then PPh_3 (4170.3 mg, 15.9 mmol, 300 mol%) was added to the solution. The reaction mixture was gradually warmed to room temperature and stirred overnight. The solution was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title compound **10** in 83% yield (1925.6 mg, 4.39 mmol).

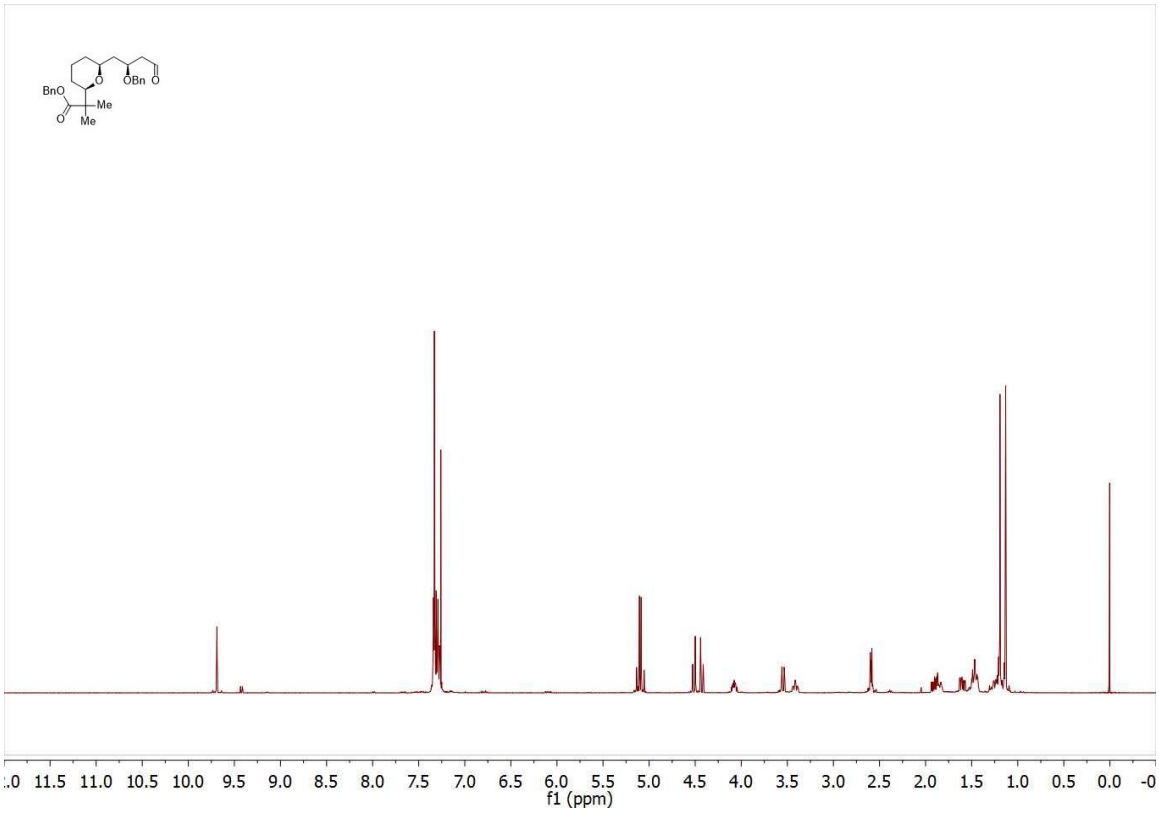
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, *J* = 2.2 Hz, 1H), 7.36–7.26 (m, 10H), 5.12 (d, *J* = 12.7 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.12–4.03 (m, 1H), 3.55 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.45–3.38 (m, 1H), 2.62–2.56 (m, 2H), 1.95–1.81 (m, 2H), 1.65–1.56 (m, 1H), 1.51–1.42 (m, 3H), 1.32–1.20 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H).

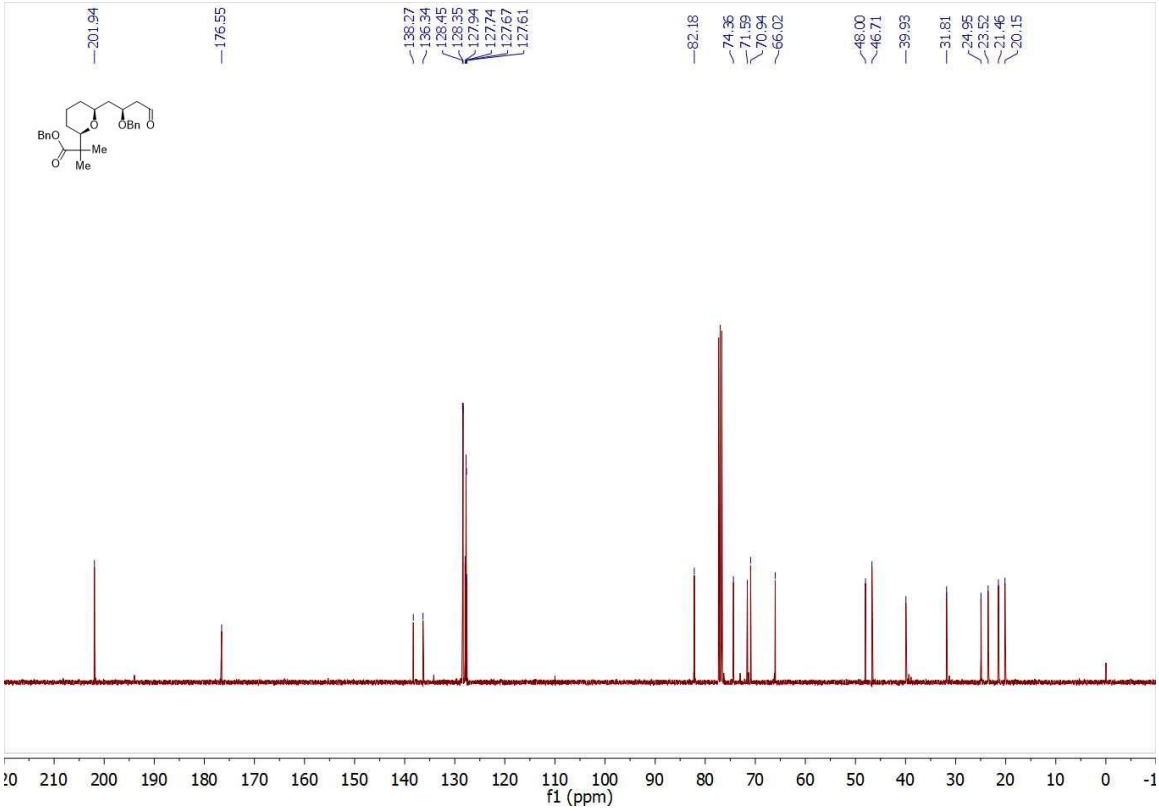
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 176.6, 138.3, 136.3, 128.5, 128.4, 127.9, 127.7, 127.7, 127.6, 82.2, 74.4, 71.6, 70.9, 66.0, 48.0, 46.7, 39.9, 31.8, 25.0, 23.5, 21.5, 20.2.

HRMS (ESI) Calcd. for $C_{27}H_{34}O_5Na$ $[M+Na]^+$: 461.2298, Found: 461.2294.

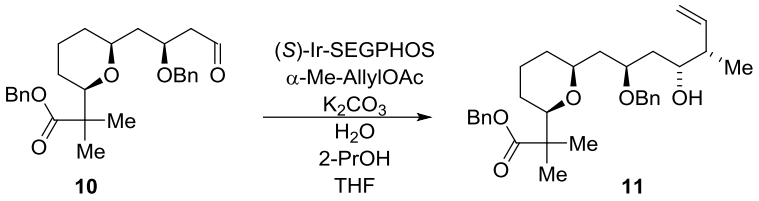
FTIR (neat): 2941, 2860, 1727, 1455, 1391, 1265, 1163, 1138, 1087, 1050, 735, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +8.33° (c 1.0, $CHCl_3$).


BnO
O
Me
Me
OBn
O
f1 (ppm)


201.94
176.55
138.27
136.34
128.45
128.35
127.94
127.74
127.67
127.61
82.18
74.36
71.59
70.94
66.02
48.00
46.71
39.93
31.81
24.95
23.52
21.46
20.15
BnO
O
Me
Me
OBn
O
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((2*R*,4*R*,5*S*)-2-(benzyloxy)-4-hydroxy-5-methylhept-6-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (11)



To a sealed tube under an argon atmosphere charged with aldehyde **10** (200.0 mg, 0.46 mmol, 100 mol%), (*S*)-Ir-SEGPHOS (23.5 mg, 0.023 mmol, 5.0 mol%), 2-PrOH (55.3 mg, 0.92 mmol, 200 mol%), K_2CO_3 (31.8 mg, 0.23 mmol, 50 mol%) and H_2O (41.4 mg, 2.30 mmol, 500 mol%) was added freshly distilled THF (0.23 mL, 2.0 M) and α-Me-AllyOAc (105.0 mg, 0.92 mmol, 200 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 60 °C for 48 h. The reaction mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 30:1 to 20:1) to furnish the title compound **11** in 65% yield (148.0 mg, 0.30 mmol, 12:1 *dr*).

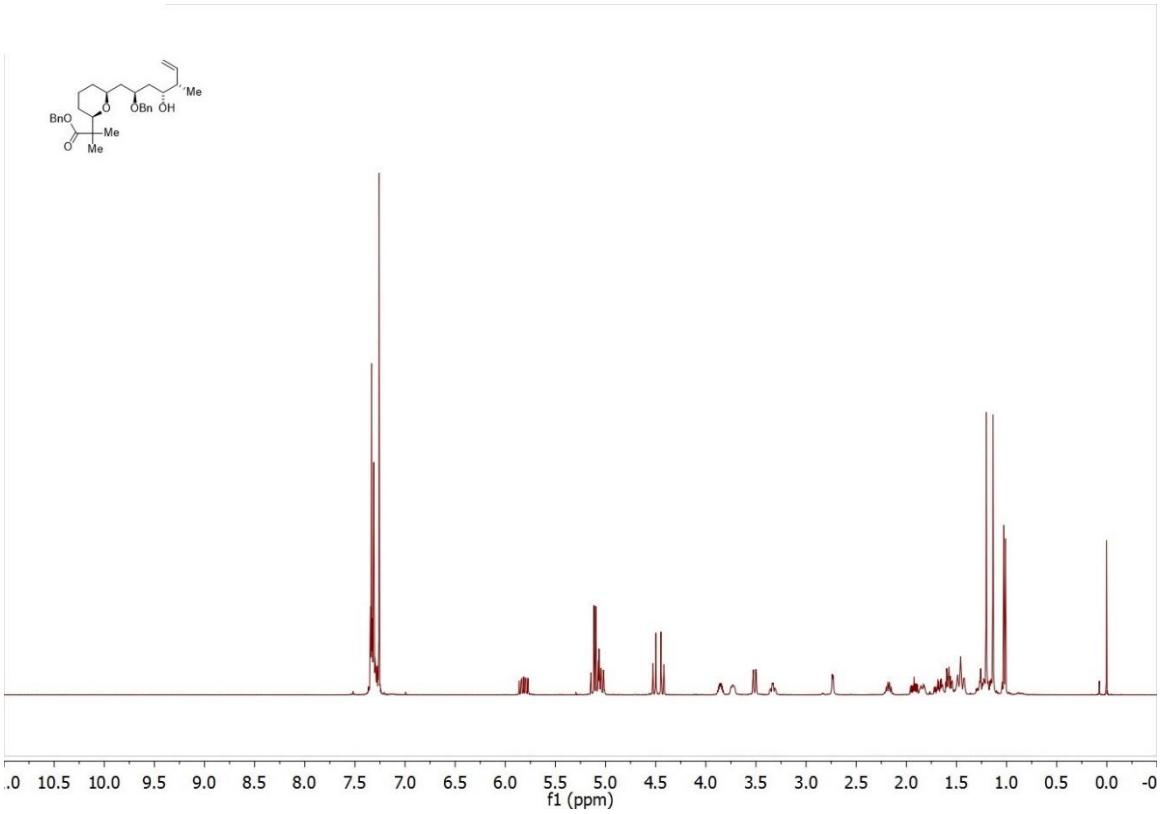
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 5.87–5.76 (m, 1H), 5.16–5.00 (m, 4H), 4.54–4.40 (dd, *J* = 12.0, 11.6 Hz 2H), 3.89–3.81 (m, 1H), 3.76–3.69 (m, 1H), 3.51 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.38–3.29 (m, 1H), 2.73 (d, *J* = 3.6 Hz, 1H), 2.23–2.10 (m, 1H), 1.97–1.78 (m, 2H), 1.73–1.39 (m, 6H), 1.32–1.10 (m, 8H), 1.02 (d, *J* = 6.9 Hz, 3H).

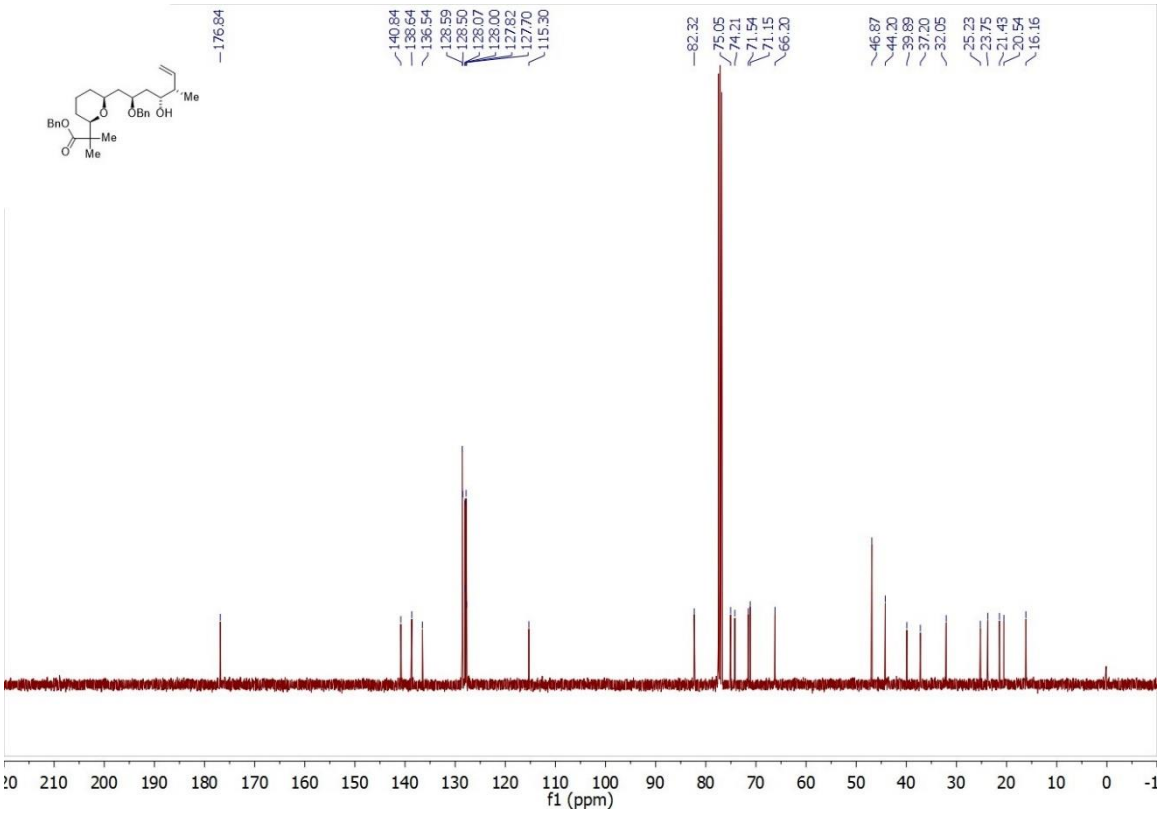
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 140.8, 138.6, 136.5, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 115.3, 82.3, 75.1, 74.2, 71.5, 71.2, 66.2, 46.9, 44.2, 39.9, 37.2, 32.1, 25.2, 23.8, 21.4, 20.5, 16.2.

HRMS (ESI) Calcd. for $C_{31}H_{42}O_5Na$ $[M+Na]^+$: 517.2924, Found: 517.2926.

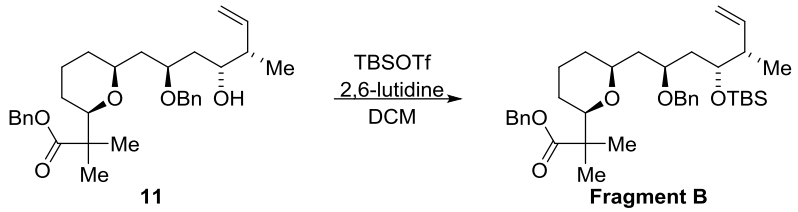
FTIR (neat): 2937, 2858, 2322, 1731, 1496, 1454, 1391, 1265, 1196, 1137, 1087, 1049, 913, 805, 734, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +8.80° (c 2.5, $CHCl_3$).


BnO
OBn
OH
Me
Me
Me
.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


176.84
140.84
138.64
136.54
128.59
128.50
128.07
128.00
127.82
127.70
115.30
82.32
75.05
74.21
71.54
71.15
66.20
46.87
44.20
39.89
37.20
32.05
25.23
23.75
21.43
20.54
16.16
BnO
OBn
OH
Me
Me
Me
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((2*S*,4*R*,5*S*)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5-methylhept-6-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate



2,6-Lutidine (91.8 mg, 0.856 mmol, 400 mol%) and TBSOTf (113.1 mg, 0.428 mmol, 200 mol%) were added to a solution of alcohol **11** (106.0 mg, 0.214 mmol, 100 mol%) in DCM (3.6 mL, 0.06 M) at 0 °C. After stirring for 3 h, the reaction mixture was diluted with DCM (4 mL) and washed with sat. NH_4Cl solution (10 mL). The aqueous layer was extracted with DCM (3 X 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1) to furnish the title compound **Fragment B** in 90% yield (117.3 mg, 0.193 mmol).

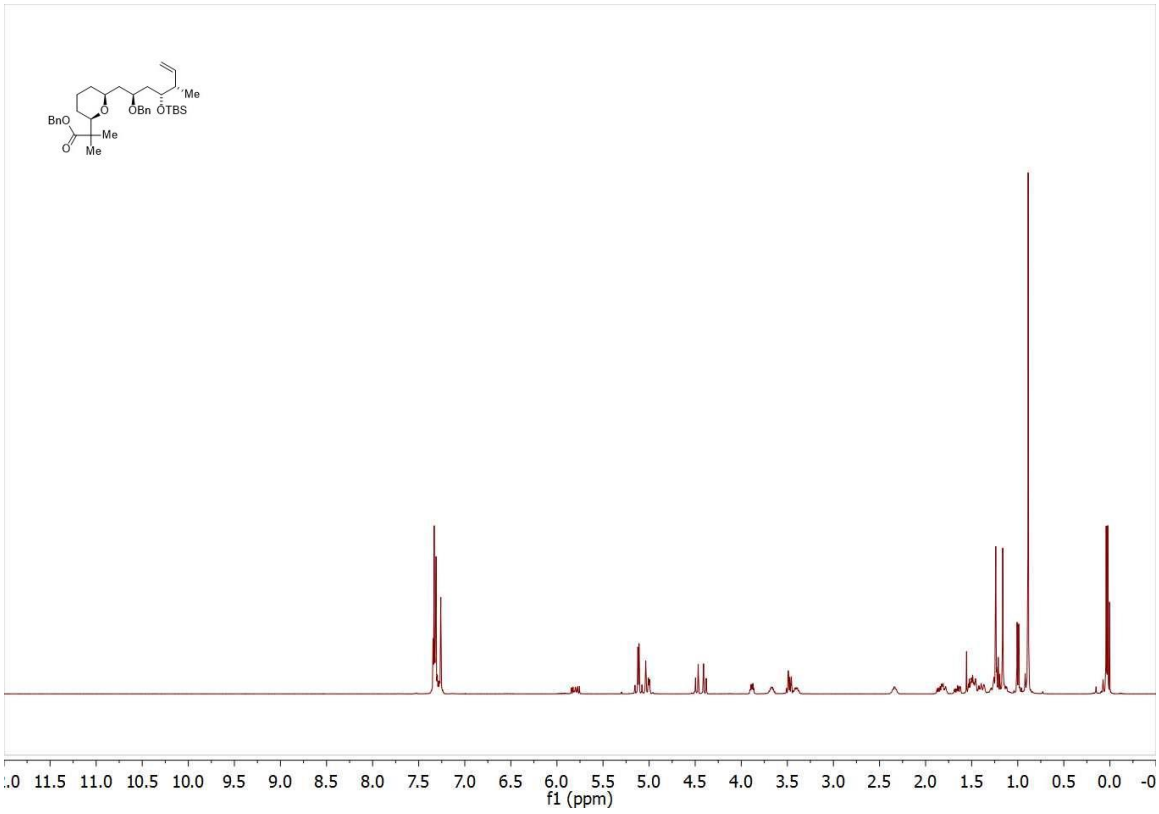
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.86–5.74 (m, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.05–4.98 (m, 2H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.91–3.85 (m, 1H), 3.71–3.63 (m, 1H), 3.51–3.45 (m, 1H), 3.40 (m, 1H), 2.39–2.30 (m, 1H), 1.90–1.76 (m, 2H), 1.71–1.61 (m, 1H), 1.55–1.35 (m, 5H), 1.31–1.10 (m, 8H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.03 (d, *J* = 6.6 Hz, 6H).

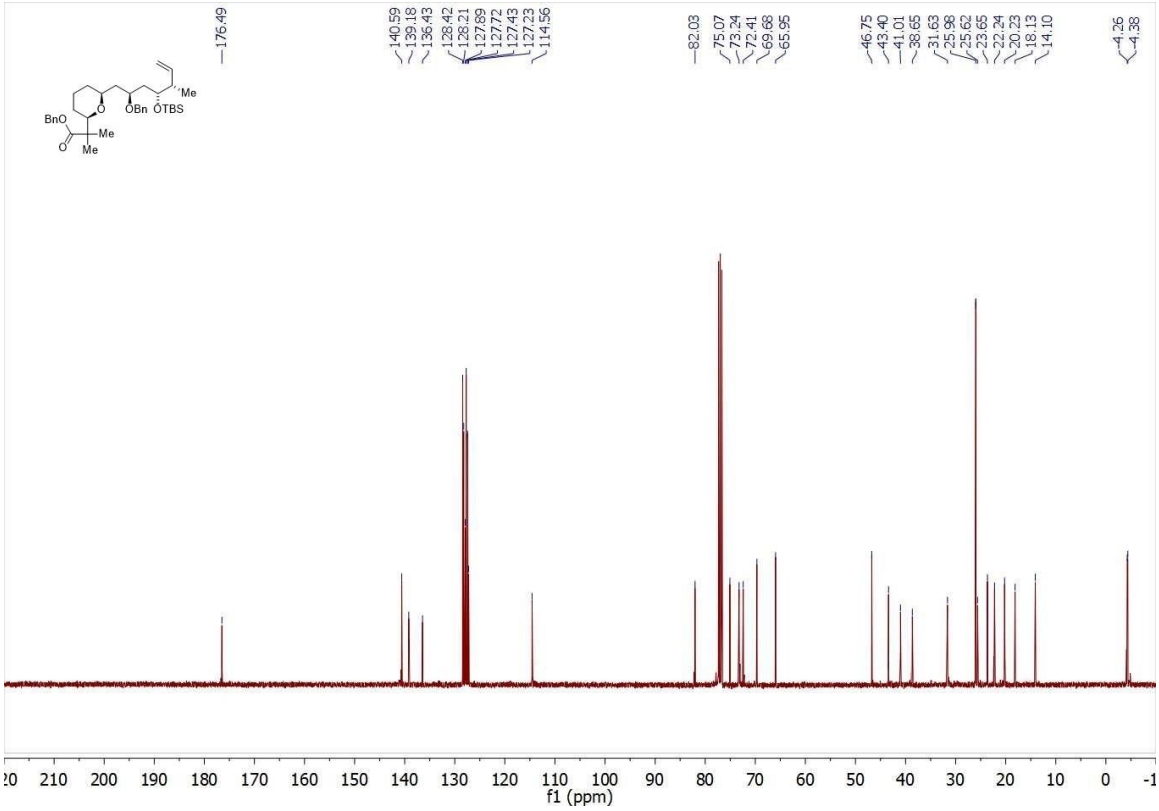
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 140.6, 139.2, 136.4, 128.4, 128.2, 127.9, 127.7, 127.4, 127.2, 114.6, 82.0, 75.1, 73.2, 72.4, 69.7, 66.0, 46.8, 43.4, 41.0, 38.7, 31.6, 26.0, 25.6, 23.7, 22.2, 20.2, 18.1, 14.1, -4.3, -4.4.

HRMS (ESI) Calcd. for $C_{37}H_{56}O_5SiNa$ $[M+Na]^+$: 631.3804, Found: 631.3808.

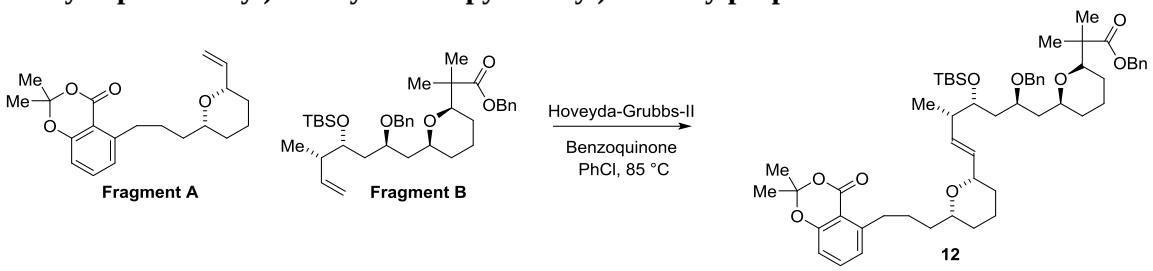
FTIR (neat): 2930, 2856, 1735, 1471, 1455, 1373, 1316, 1257, 1135, 1088, 1048, 1005, 914, 834, 774, 733, 696 cm^{-1}.

$[\alpha]^{20}_D$ = +8.67° (c 1.0, $CHCl_3$).


BnO
OBn OTBS
Me
Me
Me
f1 (ppm)


176.49
140.59
139.18
136.43
128.42
128.21
127.89
127.72
127.43
127.23
114.56
82.03
75.07
73.24
72.41
69.68
65.95
46.75
43.40
41.01
38.65
31.63
25.98
25.62
23.65
22.24
20.23
18.13
14.10
-4.26
-4.38
BnO
OBn OTBS
Me
Me
Me
f1 (ppm)

Benzyl 2-((2*S*,6*S*)-6-((2*S*,4*R*,5*S*,*E*)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-7-((2*S*,6*S*)-6-(3-(2,2-dimethyl-4-oxo-4*H*-benzo[d][1,3]dioxin-5-yl)propyl)tetrahydro-2*H*-pyran-2-yl)-5-methylhept-6-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate



A flame dried flask under an argon atmosphere was charged with fragment **A** (57.0 mg, 0.172 mmol, 150 mol%), fragment **B** (70.0 mg, 0.115 mmol, 100 mol%), 1,4-benzoquinone (1.2 mg, 0.0115 mmol, 10 mol%) and the 2nd generation Hoveyda-Grubbs catalyst (7.2 mg, 0.0115 mmol, 10 mol%). Chlorobenzene (2.90 mL, 0.04 M) was added and the solution was heated at 85 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/acetone, 30:1) to furnish the title compound **12** in 53% yield (55.5 mg, 0.061 mmol, >20:1 *E:Z*).

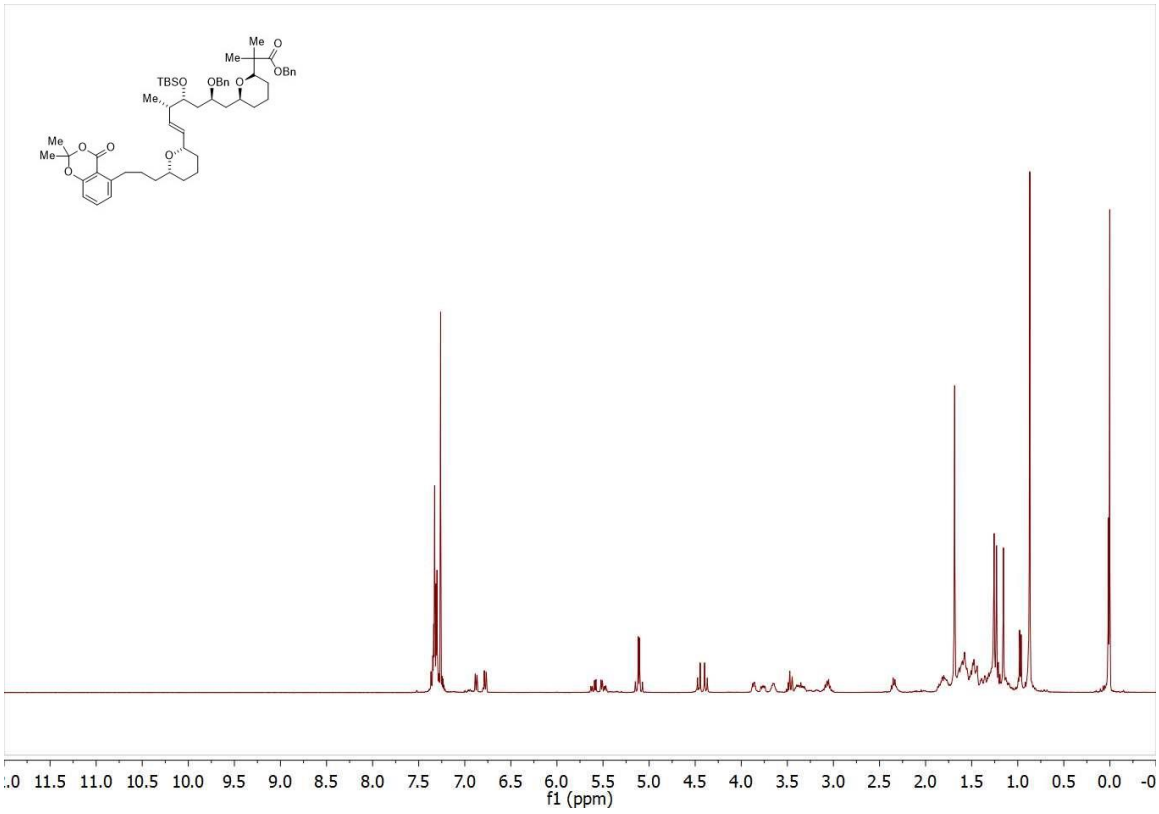
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 11H), 6.87 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.60 (dd, *J* = 15.6, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.16–5.06 (m, 2H), 4.49–4.36 (m, 2H), 3.90–3.83 (m, 1H), 3.80–3.73 (m, 1H), 3.69–3.61 (m, 1H), 3.46 (d, *J* = 10.2 Hz, 1H), 3.42–3.29 (m, 2H), 3.13–2.98 (m, 2H), 2.38–2.29 (m, 1H), 1.89–1.74 (m, 3H), 1.68 (s, 6H), 1.65–1.53 (m, 6H), 1.53–1.34 (m, 7H), 1.32–1.08 (m, 10H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H).

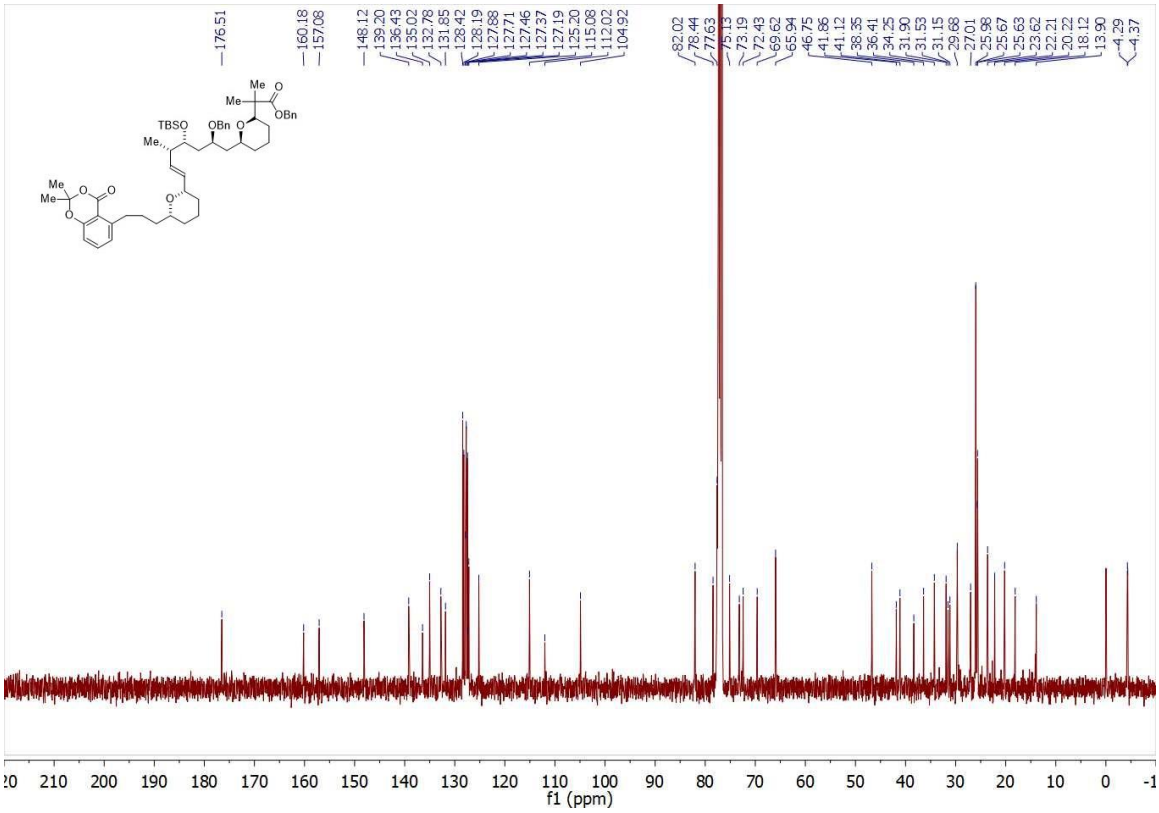
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 160.2, 157.1, 148.1, 139.2, 136.4, 135.0, 132.8, 131.9, 128.4, 128.2, 127.9, 127.7, 127.5, 127.4, 127.2, 125.2, 115.1, 112.0, 104.9, 82.0, 78.4, 77.6, 75.1, 73.2, 72.4, 69.6, 65.9, 46.8, 41.9, 41.1, 38.4, 36.4, 34.3, 31.9, 31.5, 31.2, 29.7, 27.0, 26.0, 25.7, 25.6, 23.6, 22.2, 20.2, 18.1, 13.9, -4.3, -4.4.

HRMS (ESI) Calcd. for $C_{55}H_{78}O_9SiNa$ $[M+Na]^+$: 933.5307, Found: 933.5309.

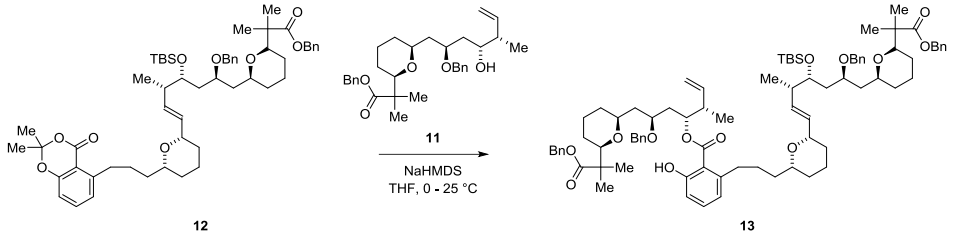
FTIR (neat): 2932, 2850, 1737, 1606, 1582, 1478, 1468, 1453, 1388, 1378, 1305, 1271, 1208, 1111, 1072, 1044, 967, 927, 807, 749, 689 cm^{-1}.

$[\alpha]^{20}_D$ = -10.00° (c 0.2, $CHCl_3$).


TBSO
OBn
OBn
Me
Me
Me
Me
O
O
O
O
O
O
O
O
O
..0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


176.51
160.18
157.08
148.12
139.20
136.43
135.02
132.78
131.85
128.42
128.19
127.88
127.71
127.46
127.37
127.19
125.20
115.08
112.02
104.92
82.02
78.44
77.63
75.13
73.19
72.43
69.62
65.94
46.75
41.86
41.12
38.35
36.41
34.25
31.90
31.53
31.15
29.68
27.01
25.98
25.67
25.63
23.62
22.21
20.22
18.12
13.90
-4.29
-4.37
TBSO
OBn
OBn
Me
Me
Me
Me
O
O
O
O
O
O
O
O
O
:0 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*S*,*E*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-1-en-1-yl)tetrahydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenzoate (13)



A flame dried flask under an argon atmosphere was charged with alcohol **11** (37.1 mg, 0.0751 mmol, 120 mol%) in THF (1.25 mL, 0.05 M) at 0 °C. NaHMDS (0.313 mL, 0.313 mmol, 500 mol%) was added dropwise at 0 °C. After stirring for 30 min, the alkene **12** (57.0 mg, 0.0625 mmol, 100 mol%) in dry THF (0.6 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h and then quenched with saturated aqueous NH_4Cl (5.0 mL). The resulting mixture was extracted with ether (3 X 5.0 mL). The combined organic extracts were washed with brine (15.0 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 30:1 to 15:1) to furnish the title compound **13** in 80% yield (67.4 mg, 0.05 mmol).

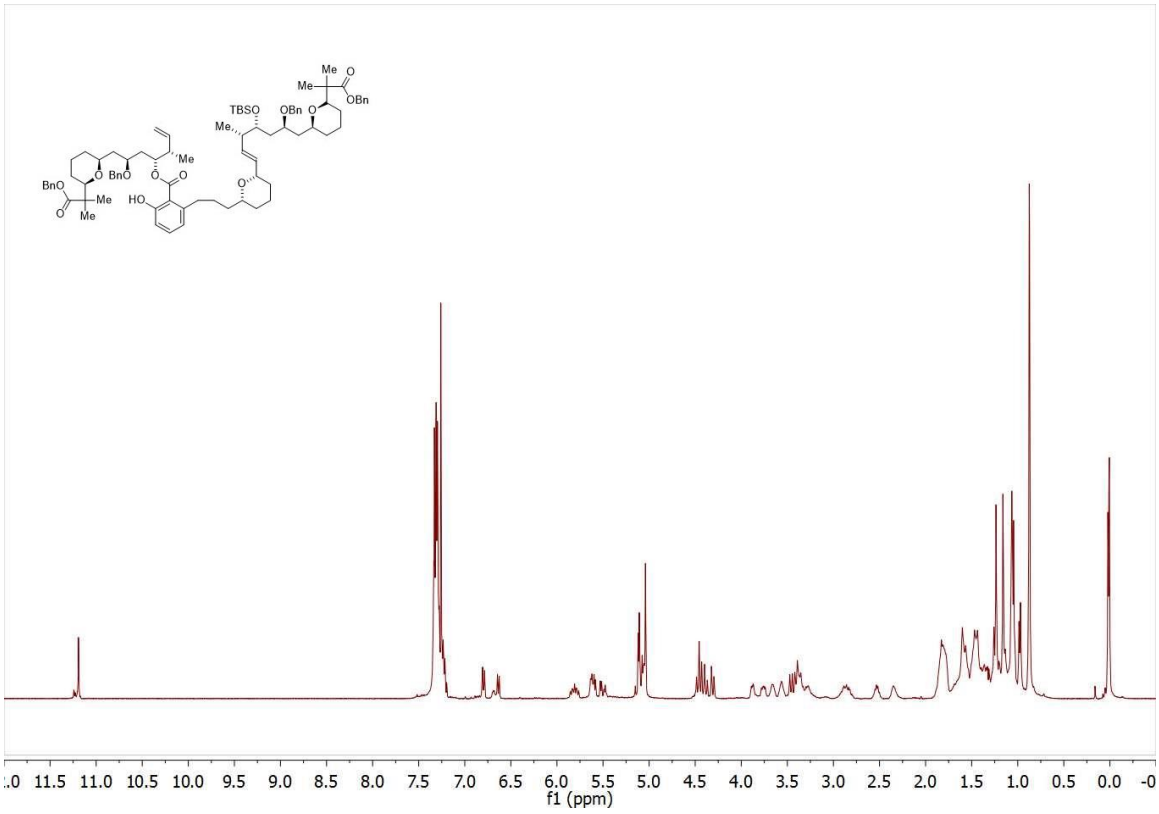
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.35–7.21 (m, 21H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.87–5.76 (m, 1H), 5.65–5.57 (m, 2H), 5.55–5.45 (m, 1H), 5.13–5.02 (m, 6H), 4.49–4.28 (m, 4H), 3.91–3.84 (m, 1H), 3.76 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.69–3.63 (m, 1H), 3.60–3.53 (m, 1H), 3.51–3.22 (m, 5H), 2.95–2.78 (m, 2H), 2.58–2.49 (m, 1H), 2.39–2.30 (m, 1H), 1.90–1.74 (m, 7H), 1.70–1.52 (m, 7H), 1.52–1.30 (m, 11H), 1.23 (s, 6H), 1.16 (d, *J* = 1.4 Hz, 6H), 1.06 (m, 9H), 1.01–0.95 (m, 2H), 0.88 (s, 9H), 0.01 (s, 6H).

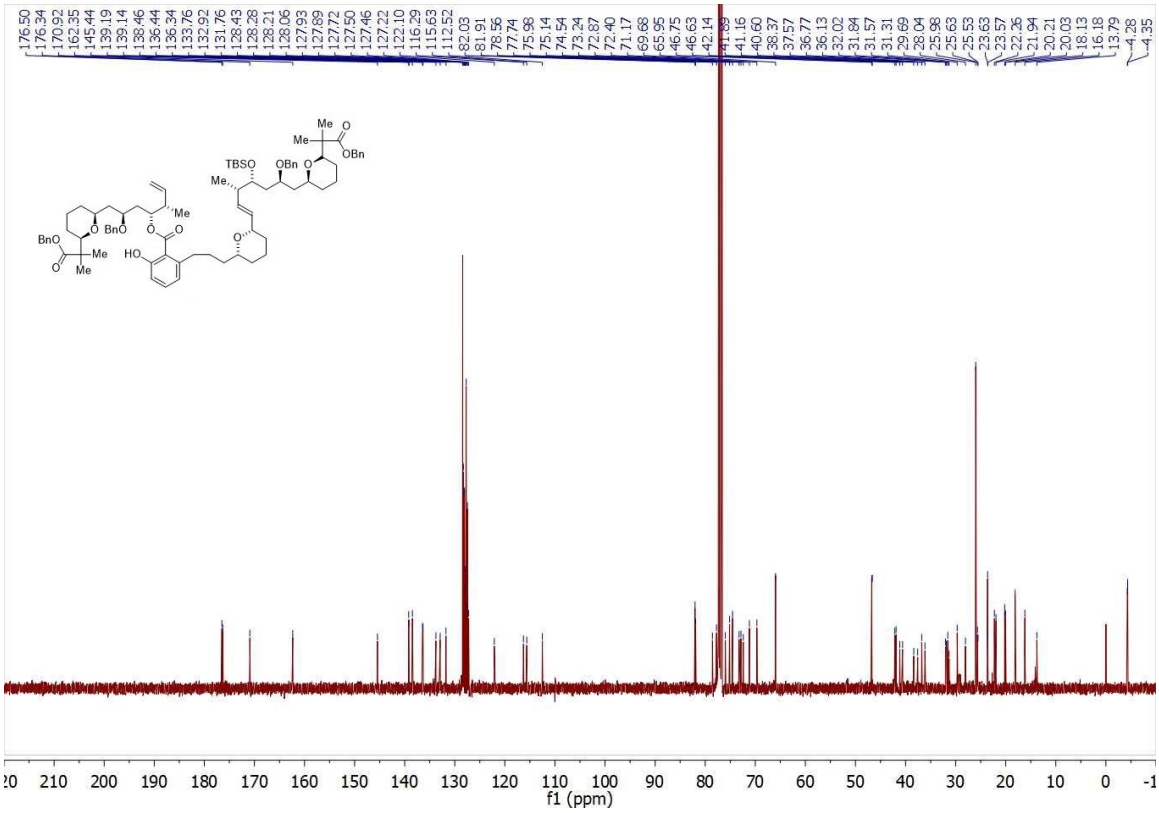
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 176.3, 170.9, 162.4, 145.4, 139.2, 139.1, 138.5, 136.4, 136.3, 133.8, 132.9, 131.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 127.7, 127.5, 127.5, 127.2, 122.1, 116.3, 115.6, 112.5, 82.0, 81.9, 78.6, 77.7, 76.0, 75.1, 74.5, 73.2, 72.9, 72.4, 71.2, 69.7, 66.0, 46.8, 46.6, 42.1, 41.9, 41.2, 40.6, 38.4, 37.6, 36.8, 36.1, 32.0, 31.8, 31.6, 31.3, 29.7, 28.0, 26.0, 25.6, 25.5, 23.6, 23.6, 22.3, 21.9, 20.2, 20.0, 18.1, 16.2, 13.8, -4.3, -4.4.

HRMS (ESI) Calcd. for $C_{83}H_{114}O_{13}SiNa$ $[M+Na]^+$: 1369.7921, Found: 1369.7918.

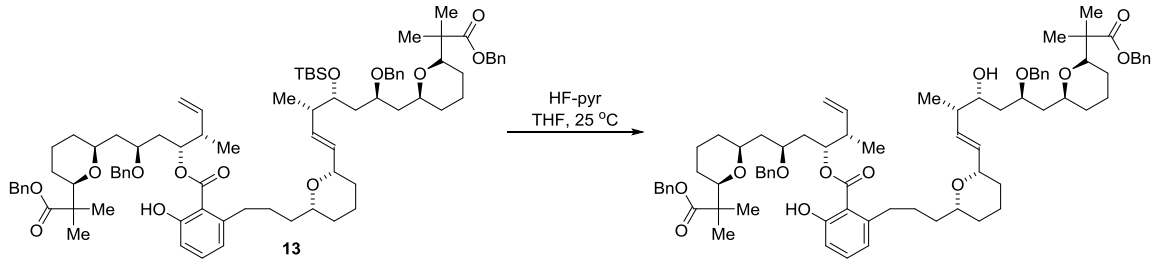
FTIR (neat): 2934, 2856, 1730, 1610, 1549, 1453, 1371, 1251, 1214, 1087, 1048, 1028, 896, 827, 752, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +12.70° (c 0.5, $CHCl_3$).


TBSO
OBn
BnO
BnO
HO
f1 (ppm)


TBSO
OBn
BnO
BnO
HO
f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*R*,*E*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-hydroxy-3-methylhept-1-en-1-yl)tetrahydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenzoate



To a solution of alkene **13** (30 mg, 0.022 mmol, 100 mol%) in THF (0.6 mL, 0.037 M) was added HF-pyridine (0.016 mL, 22.0 mmol, 1000 eq.) and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ (10 mL) and extracted with ether (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 10:1 to 5:1) to furnish the title compound in 90% yield (24.7 mg, 0.020 mmol).

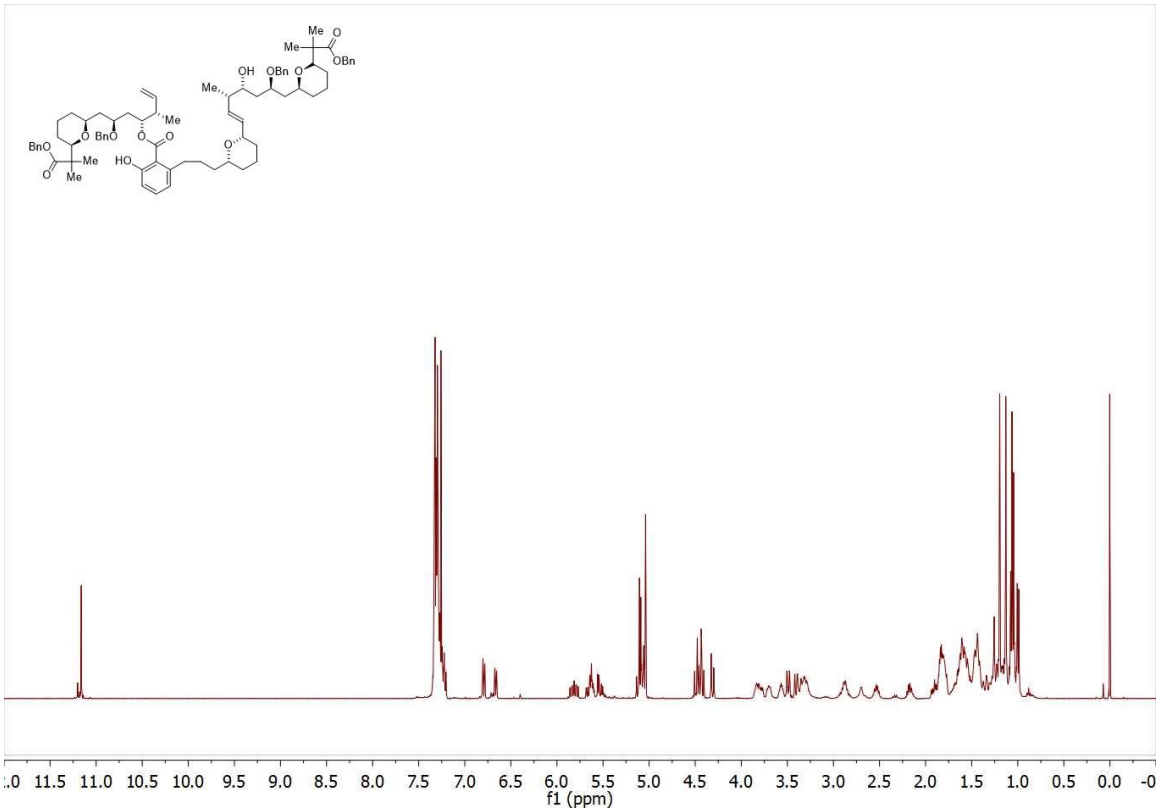
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 7.36–7.20 (m, 21H), 6.79 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.66 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.89–5.76 (m, 1H), 5.70–5.58 (m, 2H), 5.57–5.49 (m, 1H), 5.14–5.03 (m, 6H), 4.52–4.29 (m, 4H), 3.88–3.75 (m, 2H), 3.74–3.65 (m, 1H), 3.61–3.53 (m, 1H), 3.52–3.46 (m, 1H), 3.43–3.25 (m, 4H), 2.95–2.81 (m, 2H), 2.70 (s, 1H), 2.58–2.49 (m, 1H), 2.22–2.12 (m, 1H), 1.95–1.74 (m, 7H), 1.73–1.50 (m, 10H), 1.50–1.35 (m, 7H), 1.30–1.17 (m, 6H), 1.17–1.11 (m, 6H), 1.11–1.02 (m, 9H), 1.00 (d, *J* = 6.8 Hz, 3H).

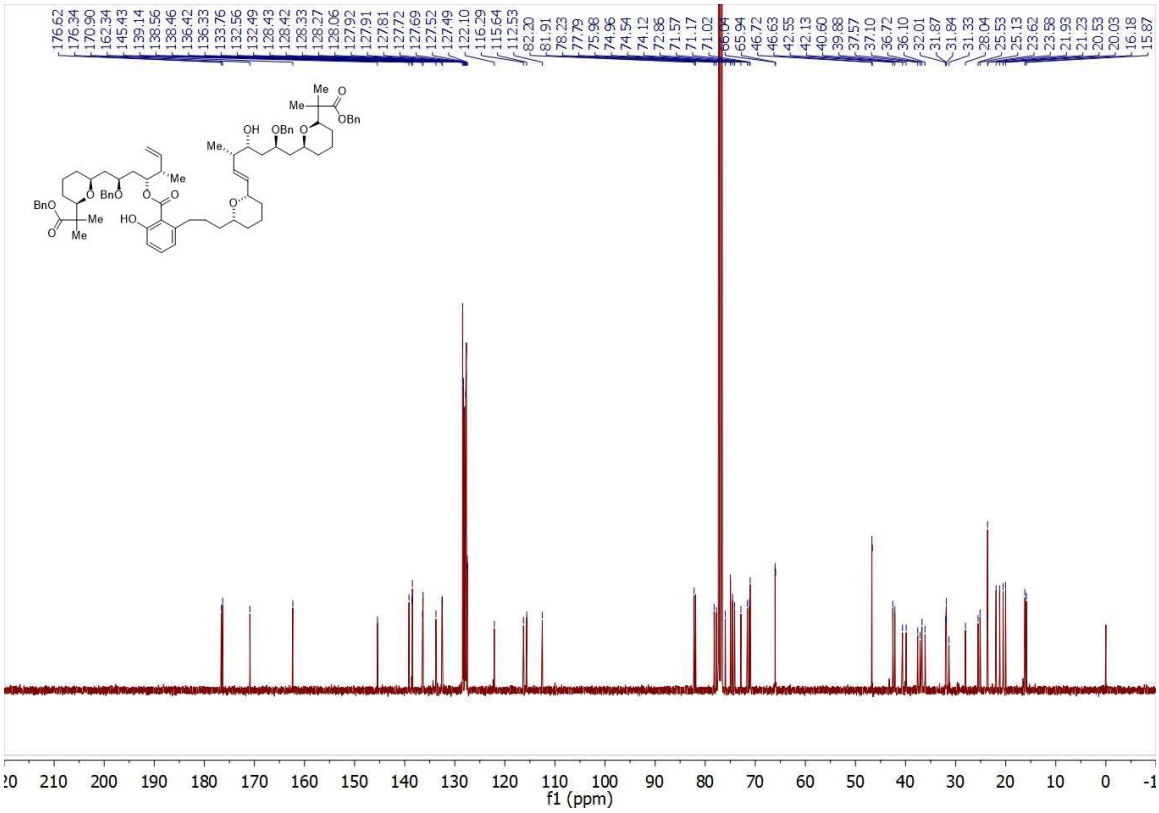
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 176.3, 170.9, 162.3, 145.4, 139.1, 138.6, 138.5, 136.4, 136.3, 133.8, 132.6, 132.5, 128.4, 128.4, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 127.5, 127.5, 122.1, 116.3, 115.6, 112.5, 82.2, 81.9, 78.2, 77.8, 76.0, 75.0, 74.5, 74.1, 72.9, 71.6, 71.2, 71.0, 66.0, 65.9, 46.7, 46.6, 42.6, 42.1, 40.6, 39.9, 37.6, 37.1, 36.7, 36.1, 32.0, 31.9, 31.8, 31.3, 28.0, 25.5, 25.1, 23.6, 23.6, 21.9, 21.2, 20.5, 20.0, 16.2, 15.9.

HRMS (ESI) Calcd. for $C_{77}H_{100}O_{13}Na$ $[M+Na]^+$: 1255.7056, Found: 1255.7037.

FTIR (neat): 2931, 2856, 1731, 1652, 1454, 1373, 1311, 1263, 1213, 1163, 1139, 1086, 1048, 1028, 1017, 734, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +6.00° (c 1.0, $CHCl_3$).


Me
Me
O
OBn
OH
OBn
O
Me
Me
BnO
O
BnO
O
O
BnO
O
Me
Me
HO
O
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


176.62
176.34
170.90
162.34
145.43
139.14
138.56
138.46
136.42
136.33
133.76
132.56
132.49
128.43
128.42
128.33
128.27
128.06
127.92
127.91
127.81
127.72
127.69
127.52
127.49
122.10
116.29
115.64
112.53
82.20
81.91
78.23
77.79
75.98
74.96
74.54
74.12
72.86
71.57
71.17
71.02
66.04
65.94
46.72
46.63
42.55
42.13
40.60
39.88
37.57
37.10
36.72
36.10
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31.33
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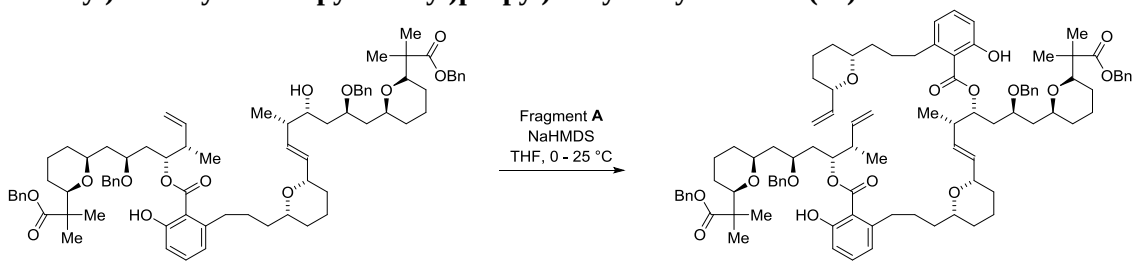
25.53
25.13
23.62
23.58
21.93
21.23
20.53
20.03
16.18
15.87
Me
Me
O
OBn
OH
OBn
O
Me
Me
BnO
O
BnO
O
O
BnO
O
Me
Me
HO
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetra-hydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*S*,*E*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-((2-hydroxy-6-(3-((2*S*,6*S*)-6-vinyltetrahydro-2*H*-pyran-2-yl)propyl)benzoyl)oxy)-3-methylhept-1-en-1-yl)tetra-hydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenzoate (14)



14

A flame dried flask was charged with alcohol (70.0 mg, 0.0567 mmol, 100 mol%) in THF (1.13 mL, 0.05 M) at 0 °C. NaHMDS (0.284 mL, 0.284 mmol, 500 mol%) was added dropwise at 0 °C. After stirring for 30 min, fragment **A** (74.9 mg, 0.227 mmol, 400 mol%) in dry THF (0.6 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h and then quenched with saturated aqueous NH_4Cl (5.0 mL). The resulting mixture was extracted with ether (3 X 5.0 mL). The combined organic extracts were washed with brine (15.0 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 6:1) to furnish the title product **14** in 85% yield (72.6 mg, 0.048 mmol).

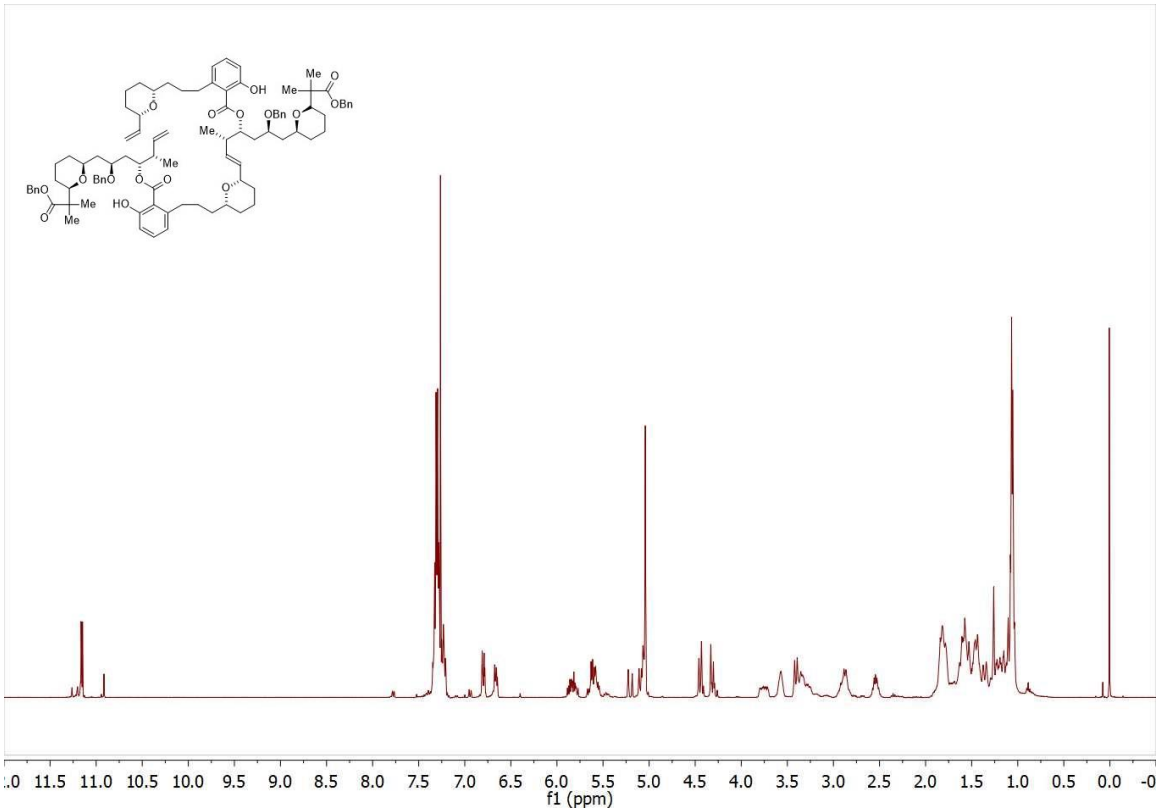
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), δ 11.14 (s, 1H), 7.36–7.19 (m, 22H), 6.82–6.77 (m, 2H), 6.69–6.63 (m, 2H), 5.90–5.75 (m, 2H), 5.67–5.52 (m, 4H), 5.24–5.00 (m, 8H), 4.48–4.40 (m, 2H), 4.34–4.25 (m, 2H), 3.82–3.69 (m, 2H), 3.61–3.53 (m, 2H), 3.44–3.21 (m, 6H), 2.97–2.79 (m, 4H), 2.60–2.48 (m, 2H), 1.89–1.73 (m, 11H), 1.66–1.32 (m, 21H), 1.30–1.00 (m, 26H).

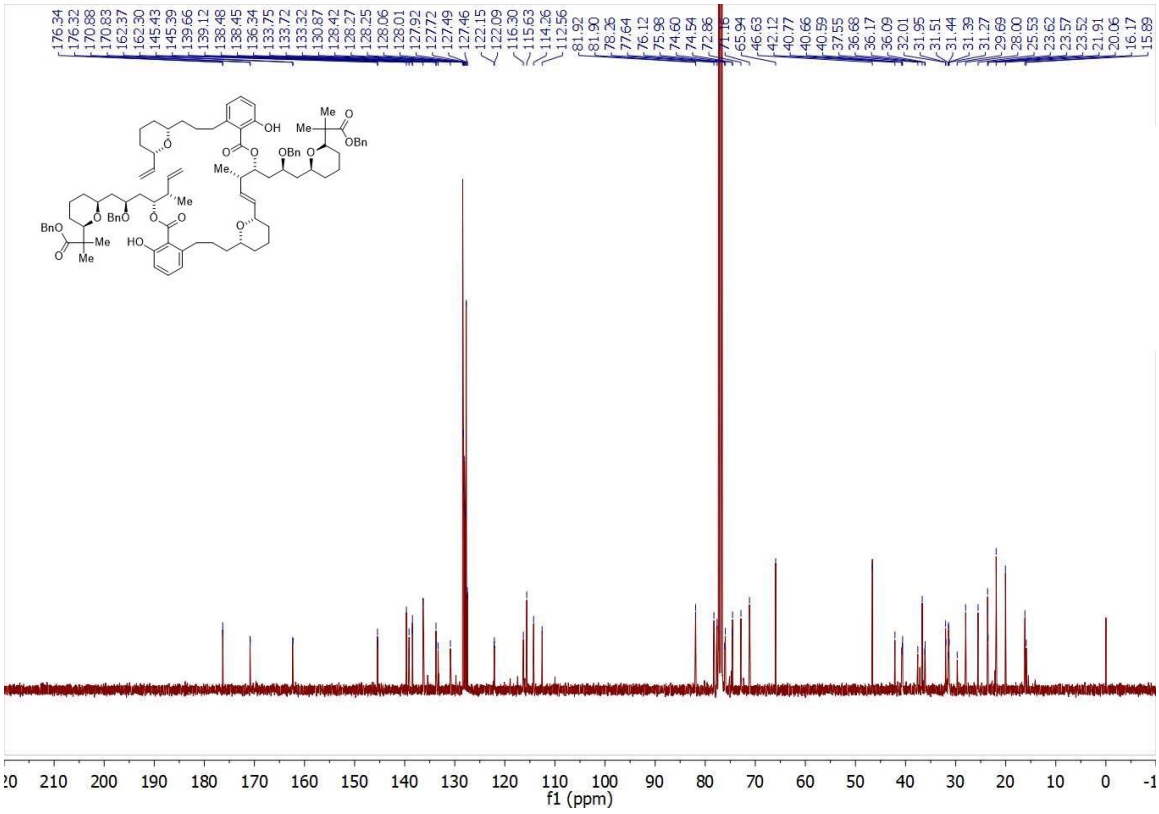
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.3, 170.9, 170.8, 162.4, 162.3, 145.4, 145.4, 139.7, 139.1, 138.5, 138.5, 136.3, 133.8, 133.7, 133.3, 130.9, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 127.5, 122.2, 122.1, 116.3, 115.6, 114.3, 112.6, 81.9, 81.9, 78.3, 77.6, 76.1, 76.0, 74.6, 74.5, 72.9, 71.2, 65.9, 46.6, 42.1, 40.8, 40.7, 40.6, 37.6, 36.7, 36.2, 36.1, 32.0, 32.0, 31.5, 31.4, 31.4, 31.3, 29.7, 28.0, 25.5, 23.6, 23.6, 23.5, 21.9, 20.1, 16.2, 15.9.

HRMS (ESI) Calcd. for $C_{94}H_{120}O_{16}Na$ $[M+Na]^+$: 1527.8469, Found: 1527.8443.

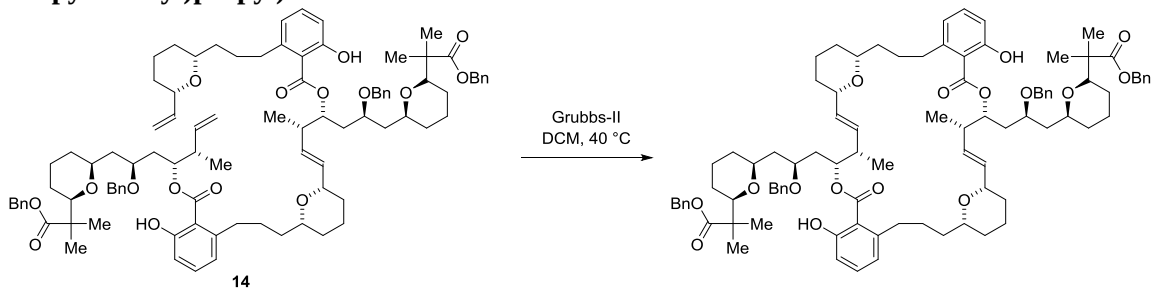
FTIR (neat): 2936, 2860, 1731, 1652, 1605, 1449, 1366, 1310, 1250, 1214, 1164, 1088, 1048, 918, 816, 738, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +14.70° (c 1.0, $CHCl_3$).


f1 (ppm)


f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-hydroxy-6-(3-((2*S*,6*S*)-6-vinyltetra-hydro-2*H*-pyran-2-yl)propyl)benzoate dimer



14

Diene **14** (30.0 mg, 0.02 mmol, 100 mol%) and Grubbs' second generation catalyst (1.70 mg, 0.002 mmol, 10 mol%) were dissolved in dry DCM (6.70 mL, 0.003 M) and the solution was heated at 40 °C. After stirring for 10 h, the reaction was concentrated *in vacuo* and subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 6:1) to furnish the title product in 68% yield (20.1 mg, 0.0136 mmol).

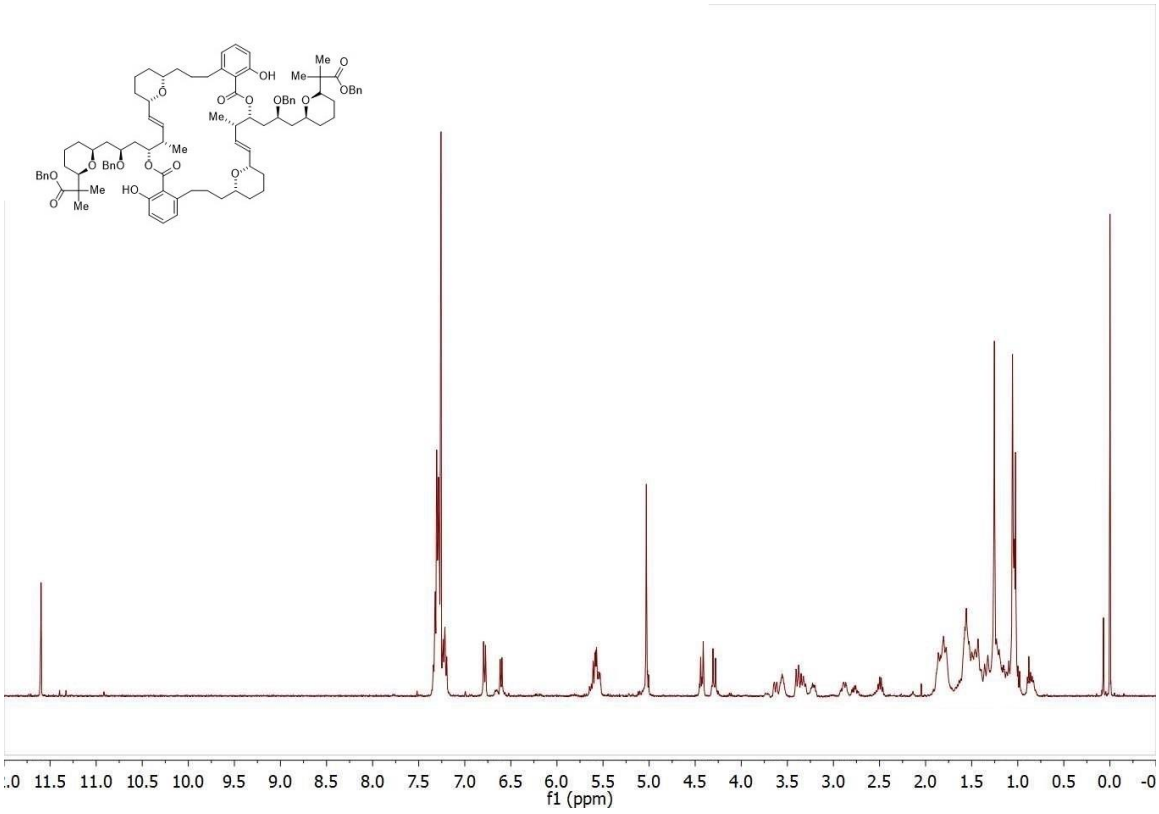
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 2H), 7.35–7.18 (m, 22H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 2H), 5.66–5.52 (m, 6H), 5.03 (s, 4H), 4.43 (dd, *J* = 11.0, 4.9 Hz, 2H), 4.30 (dd, *J* = 11.4, 5.1 Hz, 2H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.56 (s, 2H), 3.43–3.28 (m, 4H), 3.27–3.18 (m, 1H), 2.95–2.83 (m, 1H), 2.82–2.71 (m, 1H), 2.56–2.45 (m, 2H), 1.92–1.71 (m, 10H), 1.66–1.38 (m, 20H), 1.38–0.95 (m, 30H), 0.92–0.79 (m, 2H).

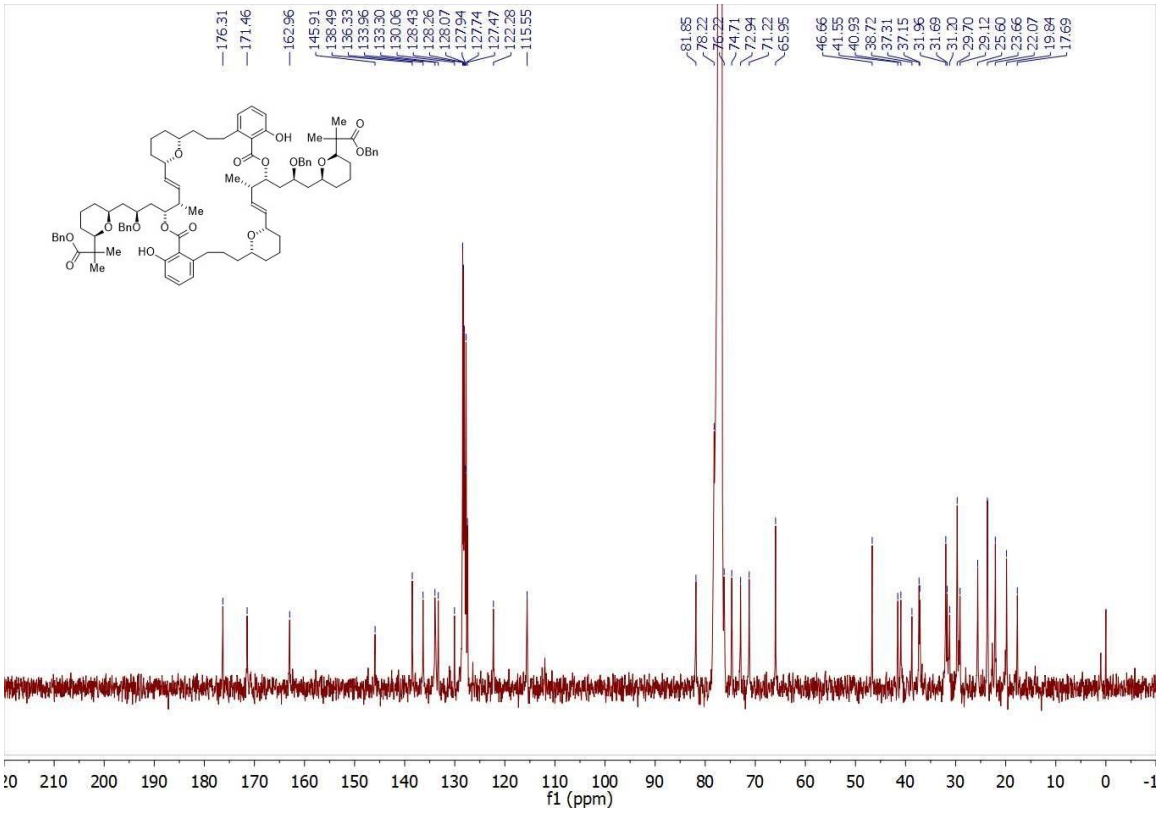
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 171.5, 163.0, 145.9, 138.5, 136.3, 134.0, 133.3, 130.1, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 122.3, 115.6, 81.9, 78.2, 76.2, 74.7, 72.9, 71.2, 66.0, 46.7, 41.6, 40.9, 38.7, 37.3, 37.2, 32.0, 31.7, 31.2, 29.7, 29.1, 25.6, 23.7, 22.1, 19.8, 17.7.

HRMS (ESI) Calcd. for $C_{92}H_{116}O_{16}Na$ $[M+Na]^+$: 1499.8156, Found: 1499.8121.

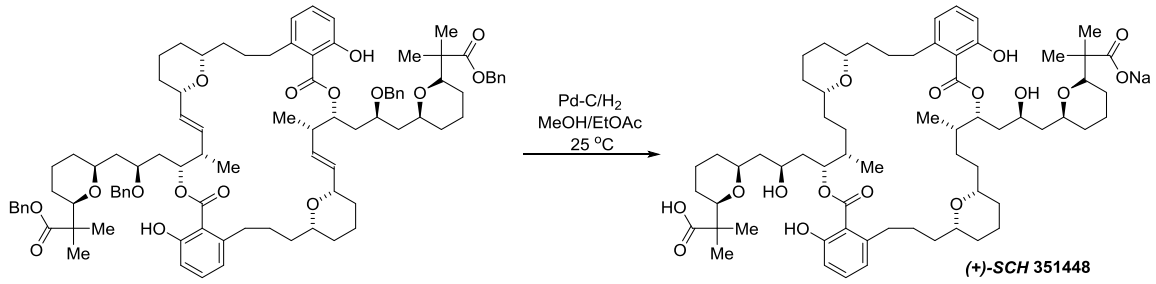
FTIR (neat): 2918, 2603, 2359, 2205, 2158, 2106, 2091, 2052, 2037, 1733, 1714, 1698, 1651, 1574, 1537, 1454, 1253, 837 cm^{-1}.

$[\alpha]^{20}_D$ = +28.70° (c 0.5, $CHCl_3$).


f1 (ppm)


176.31
171.46
162.96
145.91
138.49
136.33
133.96
133.30
130.06
128.43
128.26
128.07
127.94
127.74
127.47
122.28
115.55
81.85
78.22
76.22
74.71
72.94
71.22
65.95
46.66
41.55
40.93
38.72
37.31
37.15
31.96
31.69
31.20
29.70
29.12
25.60
23.66
22.07
19.84
17.69
f1 (ppm)

(+)-SCH 351448



To a flask charged with diene (10.0 mg, 0.0067 mmol, 100 mol%) and Pd/C (10% w/w, 1.4 mg, 20 mol%), was added EtOAc (1 mL) and MeOH (3 mL). The reaction mixture was stirred under 1 atm H_2 (balloon) for 8 h. The solution was filtered and the filtrate was concentrated in vacuo. The residue was diluted with 5 mL of hexane, and then washed with 2 mL of a 4 N HCl solution saturated with NaCl. The aqueous layer was extracted with 5 mL hexane. The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo* to afford crude (+)-SCH 351448 in 65% (5.0 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 7.5 Hz, 2H), 5.67–5.59 (m, 2H), 3.77–3.69 (m, 2H), 3.64–3.54 (m, 2H), 3.50 (d, *J* = 11.3 Hz, 2H), 3.19–3.06 (m, 6H), 2.60–2.48 (m, 2H), 2.10–2.00 (m, 2H), 1.90–1.80 (m, 4H), 1.80–1.72 (m, 2H), 1.73–1.62 (m, 6H), 1.63–1.55 (m, 4H), 1.56–1.37 (m, 22H), 1.36–1.18 (m, 10H), 1.12 (s, 6H), 1.09 (s, 6H), 1.01 (d, *J* = 6.7 Hz, 6H).

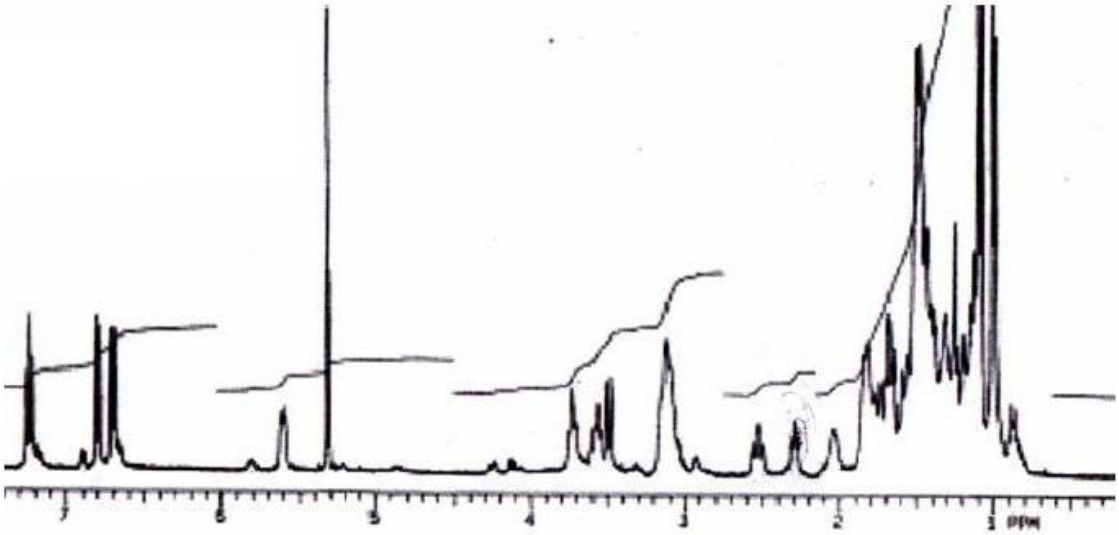
^{13}C NMR (151 MHz, CD_2Cl_2) δ 178.7, 171.1, 160.2, 145.1, 133.5, 122.4, 115.9, 115.5, 83.3, 79.2, 78.3, 78.1, 77.7, 67.5, 46.5, 43.7, 37.9, 37.5, 36.9, 36.6, 35.2, 32.9, 32.5, 32.0, 30.1, 29.5, 25.2, 24.3, 23.5, 23.2, 19.3, 15.1.

HRMS (ESI) Calcd. for $C_{64}H_{95}O_{16}Na$ $[M+Na]^+$: 1143.6591, Found: 1143.6574.

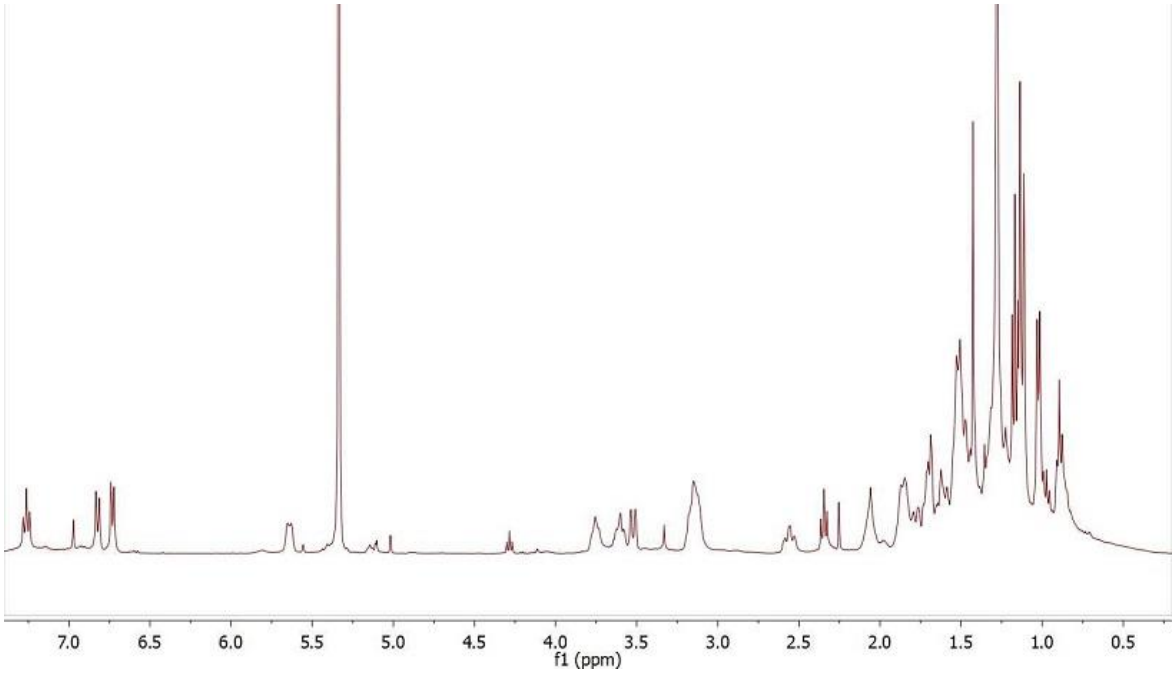
FTIR (neat): 3446, 2922, 2856, 1990, 1707, 1655, 1575, 1449, 1375, 1292, 1253, 1212, 1087, 1045 cm^{-1}.

$[\alpha]^{20}_D$ = +27.60° (c 0.3, $CHCl_3$).

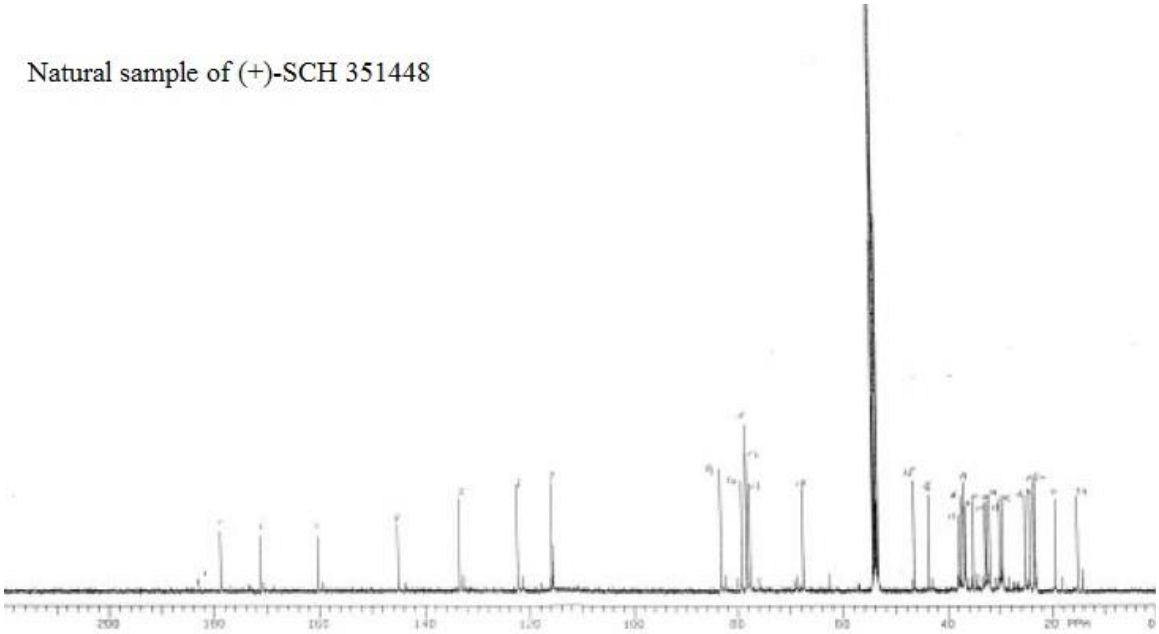
Natural sample of SCH 351448[6]



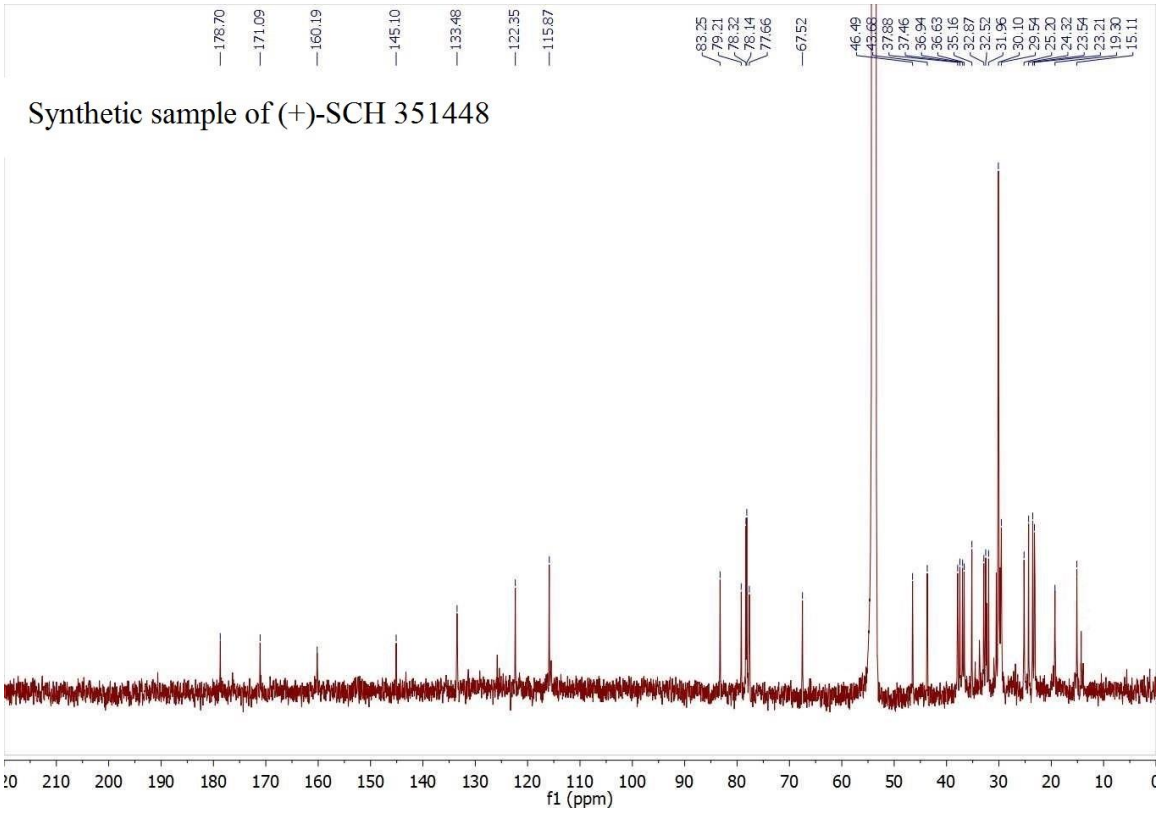
Synthetic sample of SCH 351448



Natural sample of (+)-SCH 351448



Synthetic sample of (+)-SCH 351448



^{13}C NMR comparison to the natural sample[7] of (+)-SCH 351448

Carbon #	**^{13}C (Hegde)**	**^{13}C (Krische)**
1	178.7	178.7
2	46.4	46.5
3	83.2	83.3
4	37.8	37.9
5	23.5	23.5
6	32.8	32.9
7	79.1	79.2
8	43.6	43.7
9	67.5	67.5
10	37.4	37.5
11	77.6	77.7
12	36.9	36.9
13	29.5	29.5
14	25.2	25.2
15	78.1	78.1
16	32.5	32.5
17	24.2	24.3
18	31.9	32.0
19	78.2	78.3
20	35.1	35.2
21	30.0	30.1
22	36.6	36.6
23	145.0	145.1
24	122.3	122.4
25	133.4	133.5
26	115.8	115.9
27	160.1	160.2
28	115.5	115.5
29	171.0	171.1
1-Me	19.3	19.3
1-Me	23.1	23.2
12-Me	15.0	15.1

Reference

1) Amarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals,* 6th ed., Elsevier Inc.: Oxford, UK, 2009.

2) Still, W. C.; Kahn, M; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J.-S.; Kim, H.-J.; Lee, S.-G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321.

4) Sadaba, D.; Delso, I.; Tejero, T.; Merino, P. *Tetrahedron Letters* **2011**, *52*, 5976.

5) Shiina, I.; Nagasue, H. *Tetrahedron Letters* **2002**, *43*, 5837.

6) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680.

7) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, P. R., Bond, R. W.; McPhail, A. T. *Tetrahedron Letters* **2000**, *41*, 1351.